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INVESTIGATION OF THE SHORT- AND LONG-TERM HEALTH OUTCOMES AMONG A NATIONAL COHORT OF VETERANS WITH AND WITHOUT *CLOSTRIDIOIDES DIFFICILE* INFECTION

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by

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Dedication

I dedicate this dissertation to my parents, Ellen and Rida, who so selflessly loved me and unconditionally supported me throughout this journey. Without them, and my big brothers Anthony, Jordan, and Khaled, I surely would not be who I am today. For them I will be forever thankful.

I also dedicate the completion of this research to Dr. Jennifer A. Lemmer and Dr. Bryan C. Kennedy – who ensured that I stayed on track physically, mentally, and emotionally during my time in my PhD program. They took better care of me than I did myself, and without them the completion of this research and earning the title of PhD would not be possible.

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Abstract

INVESTIGATION OF THE SHORT- AND LONG-TERM HEALTH OUTCOMES AMONG A NATIONAL COHORT OF VETERANS WITH AND WITHOUT *CLOSTRIDIOIDES DIFFICILE* INFECTION

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The University of Texas at Austin, 2021

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Clostridioides difficile infection (CDI) is an urgent public health problem in the United States (U.S.). *C. difficile* is now the most common organism implicated in healthcare-associated infections and the main source of antibiotic-associated diarrhea. Nearly half a million Americans suffer from and 29,000 die as a result of CDI annually. Importantly, CDI disproportionately affects the elderly population, with 70% of cases occurring in patients older than 65. CDI places a significant burden on patients in the short-term. While CDI commonly manifests as diarrhea, it can lead to more severe manifestations like megacolon, intestinal perforation, sepsis, or death. Importantly, CDI has been associated with impaired functional capacity in the short-term and poor overall quality of life, including physical, mental, and social functioning. CDI has also been

associated with prolonged gut microbiome dysbiosis. Dysbiosis has been previously associated with may aging- and frailty-associated conditions due to a strong biological link with the gut microbiome. Despite robust, short-term epidemiological studies, the long-term impact of CDI on healthy aging has not been investigated. To inform this knowledge gap, we addressed the hypothesis that CDI negatively affects long-term healthspan and lifespan. Our study aimed to define short- and long-term health outcomes of patients with and without CDI among a national cohort of veterans. This was a retrospective cohort study of adult patients presenting to any outpatient or inpatient Veterans Health Administration facility in the United States from October 1, 2002 to September 30, 2018. CDI patients were defined as those with an ICD-9-CM or ICD-10 code for CDI plus a positive *C. difficile* stool test and active CDI therapy. A control group was created by identifying non-CDI patients and matching 2:1 based on inpatient/outpatient visit and fiscal year. The outcomes of this study included 1 month, 3 month, 12 month, and 10-year aging-related conditions, frailty-associated conditions, and mortality. The association between CDI and these outcomes was assessed using a series of propensity score matched cohorts (1 CDI:1 control) and adjustment for covariates post-match using multivariable logistic regression. A total of 31,531 CDI cases and 81,293 non-CDI matched controls were included for analysis. CDI was significantly associated with risk for mortality at 1 month (OR 3.75, 99% CI 3.23-4.34), 3 months (OR 3.07, 99% CI 2.74-3.43), 12 months (OR 2.70, 99% CI 2.47-2.96), and 10 years (OR 1.62, 99% CI 1.34-1.97). Though numerically higher among CDI patients, the risk for chronic aging-related conditions was not statistically significant at any follow-up period,

and there was no significant association between the number of CDI episodes and the development of aging related conditions. CDI patients had higher prevalence of any frailty-related condition at short-term follow-up periods and CDI was significantly associated with the development of frailty-associated conditions at 12 months (OR 1.27, 99% CI 1.15-1.41). Finally, the number of CDI episodes was positively and significantly associated with VA frailty index at 12 months and 10 years ($p<0.0001$). In summary, CDI was associated with poor short- and long-term outcomes compared to a matched control group among a national cohort of veterans. This work is innovative because it utilizes robust data analytics on one of the world's largest clinical cohorts of CDI patients. This research is expected to have a positive impact on human health by promoting appropriate CDI prevention and treatment.

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Chapter 1: An Introduction to *Clostridioides difficile* Infection

PATHOGENESIS OF DISEASE

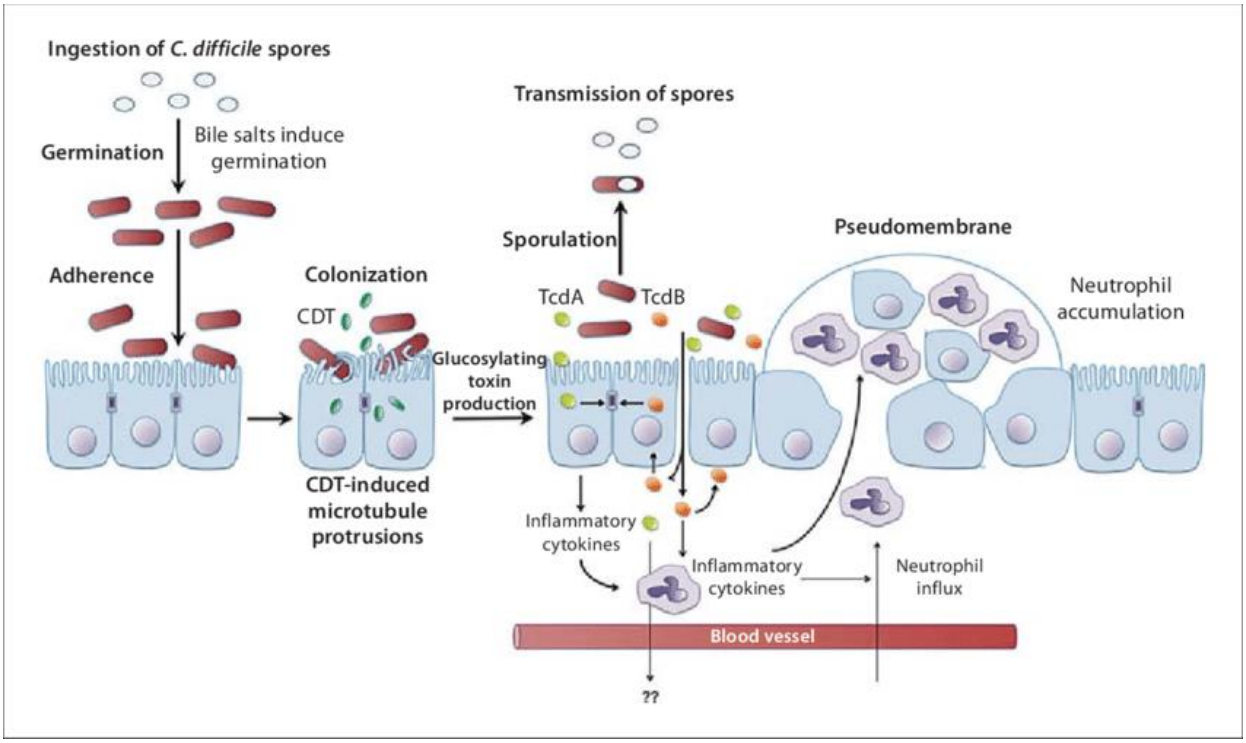
Clostridioides difficile is a gram positive, spore-forming anaerobic bacterium commonly found in the environment. *C. difficile* spores are highly tolerant to extreme temperatures, many disinfectants and chemicals, and desiccation;[1,2] therefore, spores have been previously reported in the community (e.g., post-treatment wastewater, treated compost, various soil sources),[3-5] and in healthcare facilities (e.g., toilets, bathtubs, medical instruments, personnel hands). Due to this ubiquitous nature, there are several potential environmental exposure sites for *C. difficile*, including, but not limited to hospitals and long-term care facilities, which can contribute to both asymptomatic colonization of the host and potential symptomatic infection due to transmission via the fecal-oral route.

The pathogenesis of CDI is strongly driven by a disruption in the healthy host gut microbiome. The human gut microbiome contains trillions of microbial cells that interact with the human host to prevent infection, limit accumulation of toxins, and modulate the immune response. Importantly, the microbiota are exclusively responsible for several metabolic functions, including metabolism of short chain fatty acids, organic acids and vitamins, and transformation of transforming bile salts, lipids, and amino acids.[6] A loss of protective microbes, namely due to antibiotic exposure, results in a loss of *C. difficile* colonization resistance. Once colonization is established, *C. difficile* spores can germinate and produce new vegetative cells when the conditions become favorable. For example,

the primary bile acid taurocholate promotes germination[7] while the secondary bile acid deoxycholate acts as a competitive inhibitor of taurocholate and suppressant of vegetative growth.[8]

Vegetative growth of *C. difficile* results in production of toxins, including enterotoxin A and cytotoxin B. These toxins can cause disease in the host by disrupting signal transductions of the cytoskeleton and translocating toxin into the cytosol.[9] The host's immune response to cell uptake of these virulence factors involve increased inflammation, mucosal and fluid secretion, and damage to mucosal linings, which can result in diarrhea or more severe complications like sepsis/shock, acute renal failure, ileus, perforated intestine, or megacolon in humans.[10] These responses result in symptomatic *C. difficile* infection (CDI), as described in Figure 1.1. It is important to note that toxin production is required for symptomatic infection in humans, and colonization alone does not qualify an individual as having clinical disease. Certain strains of *C. difficile* do not produce toxin;[2] thus, colonization would not pose a risk for symptomatic infection.

Figure 1.1. Microbiological pathogenesis of CDI.



Importantly, CDI is a bacterial infection that is treated with antibiotics. CDI-active antibiotics can continue to disrupt the host microbiome and prevent recovery; thus, *C. difficile* spores may persist and ultimately cause a subsequent recurrent infection (i.e., relapse) or patients may become colonized with a new strain (i.e., reinfection) due to limited colonization resistance. Approximately half of patients who recur within two months have relapse and the other half reinfection;[11] however, relapse and reinfection are regarded as clinically indistinguishable and are referred to interchangeably in a clinical setting as "recurrence."

DISEASE BURDEN AND COST

In the U.S. alone, nearly half a million people suffer from and 29,000 people die as a result of CDI annually,[4] resulting in approximately $4.8 billion in healthcare costs each year.[5] CDI disproportionately affects older adults, with approximately 70% of cases occurring in patients older than 65 years.[6] Our recent study found that CDI incidence in the elderly nearly doubled from 2001 to 2010, significantly outpacing the rise in CDI in other age groups.[7] In 2017, the U.S. saw a drop in cases and deaths, with 223,900 hospitalized patients suffering from CDI and 12,800 deaths occurring that year, though *C. difficile* is still seen as a major infectious disease threat with high antibiotic resistance potential.[12] Recent trends show a consistent reduction of CDI cases by about -4% per year from 2011 to 2017,[13] equating to an overall CDI reduction of 24%, respectively. These trends are credited to the emphasis placed on improved hospital infection control practices and subsequent reduction in overall healthcare-associated infections throughout this time period, which is further strengthened by trend data showing that healthcare-associated *C. difficile* infection decreased by approximately -6% per year (36% decrease in total) but there was no statistically significant reduction in community-associated *C. difficile* during the same time period.[13] CDI recurrence also continues to be a major concern. In 2017, there were approximately 69,800 patients who experienced a first recurrence in the U.S. (Table 1.1). The national burden of CDI in the U.S. from 2011 to 2017 is summarized in Table 1.1.

Table 1.1. Summary of the national burden of CDI in the U.S. from 2011 to 2017.[13]

Table 3. U.S. National Estimates of First Recurrences, Hospitalizations, and In-Hospital Deaths Associated with CDI, According to Epidemiologic Class, 2011–2017.*

Variable	2011	2012	2013	2014	2015	2016	2017
Estimated first recurrences							
Community-associated CDI							
No. (95% CI)	24,100 (19,000–29,300)	23,400 (19,500–27,400)	28,800 (24,900–32,800)	29,300 (24,100–34,500)	35,300 (29,700–40,900)	33,600 (29,000–38,300)	31,300 (26,600–36,000)
Incidence per 100,000 persons (95% CI)	7.9 (6.2–9.5)	7.6 (6.3–8.8)	9.2 (8.0–10.5)	9.3 (7.7–11.0)	11.1 (9.4–12.9)	10.5 (9.1–12.0)	9.7 (8.3–11.2)
Health care–associated CDI							
No. (95% CI)	60,500 (50,100–70,800)	53,900 (44,100–63,700)	48,500 (41,800–55,100)	55,600 (46,800–64,400)	58,100 (51,300–64,900)	43,500 (37,500–49,400)	38,500 (32,100–44,800)
Incidence per 100,000 persons (95% CI)	19.7 (16.3–23.0)	17.4 (14.2–20.6)	15.5 (13.4–17.7)	17.7 (14.9–20.5)	18.3 (16.2–20.5)	13.6 (11.8–15.5)	12.0 (10.0–13.9)
Estimated hospitalizations							
Community-associated CDI							
No. (95% CI)	52,500 (43,800–61,100)	61,800 (54,200–69,500)	66,000 (58,900–73,200)	71,600 (61,200–81,900)	76,300 (68,200–84,300)	79,100 (68,000–90,300)	69,900 (61,100–78,600)
Incidence per 100,000 persons (95% CI)	17.1 (14.3–19.9)	20.0 (17.5–22.4)	21.2 (18.9–23.5)	22.7 (19.4–26.0)	24.0 (21.5–26.6)	24.8 (21.3–28.3)	21.7 (19.0–24.4)
Health care–associated CDI							
No. (95% CI)	186,600 (155,500–217,600)	189,600 (165,700–213,500)	178,400 (158,300–198,500)	190,200 (171,400–209,000)	196,000 (179,700–212,300)	173,100 (158,900–187,200)	154,100 (140,700–167,400)
Incidence per 100,000 persons (95% CI)	60.7 (50.6–70.8)	61.2 (53.5–68.9)	57.2 (50.7–63.6)	60.4 (54.4–66.4)	61.8 (56.6–66.9)	54.2 (49.8–58.7)	47.9 (43.7–52.0)
Estimated in-hospital deaths							
Community-associated CDI							
No. (95% CI)	5000 (3200–6700)	5100 (3000–7100)	5700 (3600–7700)	5800 (3800–7900)	5800 (3900–7700)	7200 (3400–11,000)	4300 (2300–6300)
Incidence per 100,000 persons (95% CI)	1.6 (1.0–2.2)	1.6 (1.0–2.3)	1.8 (1.2–2.5)	1.9 (1.2–2.5)	1.8 (1.2–2.4)	2.3 (1.1–3.4)	1.3 (0.7–2.0)
Health care–associated CDI							
No. (95% CI)	25,600 (18,200–33,000)	15,300 (11,000–19,700)	16,700 (12,400–21,100)	19,000 (14,500–23,400)	23,200 (19,800–26,600)	19,500 (15,800–23,200)	16,200 (13,300–19,200)
Incidence per 100,000 persons (95% CI)	8.3 (5.9–10.7)	5.0 (3.6–6.4)	5.4 (4.0–6.8)	6.0 (4.6–7.5)	7.3 (6.2–8.4)	6.1 (5.0–7.3)	5.0 (4.1–6.0)

* Recurrence refers to the first recurrent episode, defined as a positive stool specimen within 2 to 8 weeks after the initial positive test. Hospitalization includes admission on the day of or in the 6 calendar days after diagnosis of CDI. In-hospital deaths refer to deaths that occurred during hospitalization.

CLINICAL PRESENTATION

CDI is the main cause of bacterial infectious diarrhea in nosocomial settings,[14] but the community is a major source of infection as well,[15] with sources citing up to 50% of total cases in some countries resulting from community-acquired transmission.[13,16] CDI is categorized into one of three types as defined by the Society of Hospital Epidemiologists (SHEA) and Infectious Disease Society of America (IDSA) for surveillance purposes: 1)

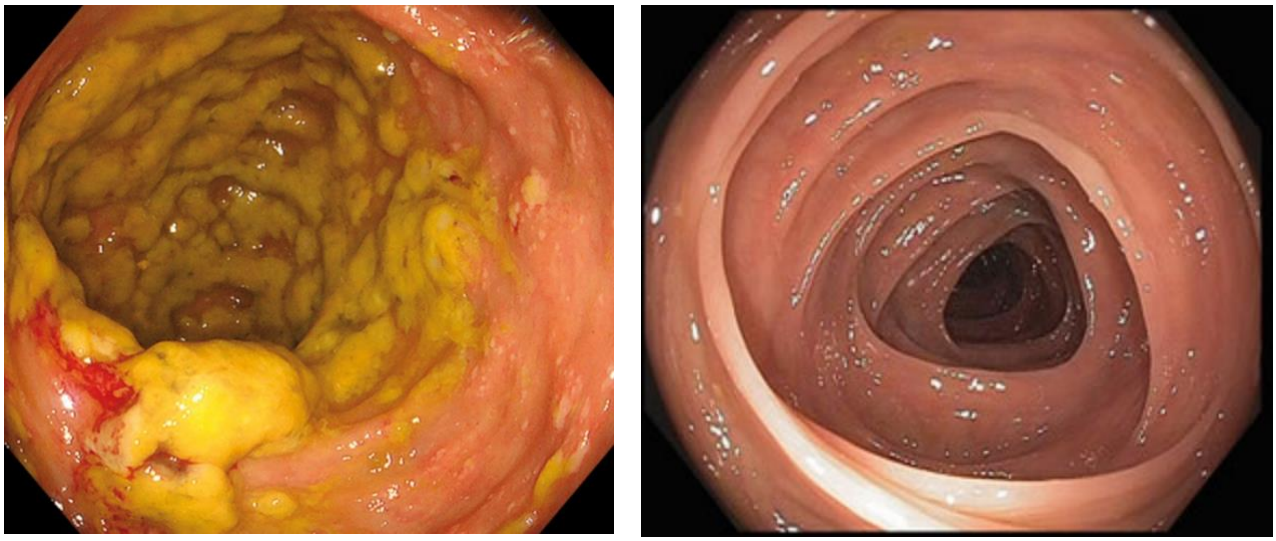
healthcare facility-onset (HO-CDI), 2) community-onset, healthcare facility-associated (CO-HCFA-CDI), and 3) community-associated (CA-CDI). Criteria for meeting these definitions are summarized in Table 1.2.

Table 1.2. Surveillance categories of CDI by the CDC Emerging Infections Program.[17]

CDI category	**Clinical definition**
Healthcare facility-onset	Positive stool specimen collected greater than 3 days after hospital admission ***OR*** present in a long-term care facility resident
Community-onset healthcare facility-associated	Positive stool specimen collected in outpatient setting ***OR*** within 3 days after hospital admission in any person with documented overnight stay in a healthcare facility (hx of hospitalization or. LTCF residency in previous 12 weeks)
Community-associated	Positive stool specimen collected in outpatient setting or within 3 days in any person with no documentation of overnight stay in a healthcare facility in previous 12 weeks

CDI primarily manifests as diarrhea but can lead to severe manifestations or even death. In a national study, Lucado et al. found that patients with CDI experienced sepsis/septicemia (26.7%), acute renal failure (23.6%), shock (8.0%), ileus (4.7%), perforated intestine (0.4%), and megacolon (0.1%).[10] Among hospitalized CDI patients, mortality ranges from 14% to 25% at 30 days, 17% to 22% at 60 days, and 23% to 29% at 90 days following CDI diagnosis.[18-25]Among critically ill patients, 30-day mortality is substantially higher (37%).[25,26]

Figure 1.2. Inflammatory response in CDI-induced pseudomembranous colitis of the colon[27] (left) compared to a healthy colon[28] (right) during colonoscopy.



Importantly, patients who experience one CDI episode are likely to experience it again. Approximately 25% of CDI patients will suffer a recurrence despite successful treatment of the initial episode.[29] Furthermore, 45% to 65% of patients who suffer one recurrent episode will have additional recurrences.[30] Recurrent CDI places a heavy burden on patients, as it increases morbidity and mortality, and diminishes quality of life. Patients with recurrent CDI experience prolonged symptoms and repeated courses of antibiotics.[31] This can lead to increased risk of adverse effects, re-hospitalization, and potential transmission to other vulnerable patients.[32] Importantly, CDI has been associated with impaired functional capacity in the short-term and poor overall quality of life, including physical, mental, and social functioning.[32,33] Garey et al. noted that patients with recurrent CDI had significantly lower quality of life overall compared to patients with a primary CDI episode within 7 days.[33] Quality of life scores consistently decreased with number of CDI episodes and increased with time since last episode. Finally, in a recent study, we found

that hospitalized patients with CDI are more likely to be discharged to a non-home location (e.g., nursing home, hospice) compared to non-CDI control patients.[34] Despite robust, short-term epidemiological studies, the long-term impact of CDI on physical and mental functioning has not been investigated.

CDI DIAGNOSIS

Clinicians can make an initial diagnosis of CDI based on clinical presentation of suspected infection, including frequent, new-onset diarrhea (defined as ≥3 loose stools per day). Presentation may also include a fever (>102 degrees), abdominal distention, and leukocytosis, according to 2017 guidelines.[35] Patients with other well-defined CDI risk factors should also be considered for further testing, as described in the next section.

Despite suspicion of infection based on clinical presentation, empiric antibiotic therapy without confirmed diagnostic test results is not appropriate, as previous literature has shown that only approximately 30% of hospitalized patients experiencing diarrhea have CDI.[11] This, however, does not apply to patients in rapid deterioration who are at high risk for CDI and may benefit from empiric therapy while awaiting diagnostic confirmation.

Diagnostic testing confirmation can occur through several tests; however, the stool test is the current gold standard. Because symptomatic infection cannot occur without the presence of toxins, tests should measure the presence of TcdA and TcdB in stool samples, which encompasses several assays, depending on the method used. A summary of diagnostic testing can be found in Table 1.3.

Table 1.3. Diagnostic testing methods for CDI with accompanying advantages and disadvantages.[11]

Diagnostic test	Completion time (est.)	Sensitivity	Advantages	Disadvantages
Tissue cytotoxic assay	48 hrs	94 – 100%	Gold standard A, B strains both detected	Higher false positive rates Technician experience can impact results
Common antigen (e.g., glutamate dehydrogenase)	15-45 min	58 – 92%	Easy use A, B strains both detected	No distinction between toxins Other anaerobes can cause cross-reactions
ELISA* Toxin A	2 hrs	80 – 99%	Easy use	No distinction between toxins
ELISA Toxin A + B	2 hrs		A, B strains both detected	Sensitivity for low-level toxins is increased
Immunochromatographic toxin A	< 1 hr	60 – 85%	Rapid test Simple use	No distinction between toxins
Anaerobic culture	72 hrs	89 – 100%	Molecular typing possible from results	No distinction between toxins
Endoscopy	2 hrs	51%	Pseudomembranous colitis diagnostic tool	Low sensitivity
Nucleic acid amplification test	2 hrs	98-99%	Rapid test Highly sensitive	Tests for toxin genes, which may not correlate with expression

*ELISA: enzyme-linked immunosorbent assay

CDI RISK FACTORS

While there are several risk factors for CDI, antibiotic therapies are now widely understood to be the most important factor in a patient's history. As the antibiotics disrupt the normal gut microbiome, the risk of *C. difficile* colonization and resulting illness from *C. difficile* increases. While risk from antibiotics vary based on a number of individual factors, studies have shown that the gut microbiome becomes disrupted, increasing CDI risk, and can occur from as little as one dose (e.g., those used to prepare for surgical procedures).[36] It is also understood that longer therapies, multiple agents, and particular classes of antibiotics can carry even higher risk for CDI due to increased gut microbiome disruption. For example, several antibiotic classes have been identified as carrying significant CDI risk; clindamycin, carbapenems, and extended-spectrum penicillins and cephalosporins more extensively cause damage to normal, protective gut microbiota.[11] Antibiotics associated with CDI risk, as well as other medications, host-related factors, and clinical characteristics and interventions that increase CDI risk are presented in Table 1.4.

Table 1.4. Pharmacologic, host-related, and clinical risk factors associated with CDI.[37]

Risk Factors	
Pharmacological: antibiotics	**Pharmacological: other**
Clindamycin *Carbapenems* *Cephalosporins (3^{rd}/4^{th} gen.)* *Fluoroquinolones* *Penicillins* *Cephalosporins (1^{st}/2^{nd} gen.)* *Trimethoprim sulfamethoxazole* *Macrolides* *Aminoglycosides* *Daptomycin* *Tetracyclines* *Vancomycin*	**Gastric acid suppressants** *Histamine 2 receptor antagonists* *Proton pump inhibitors* **Other** *Chemotherapeutic agents* *Anti-ulcer medications (non-specific)* *Non-steroidal anti-inflammatory drugs* *Corticosteroids* *Opiates (use during last CDI episode)*
Host-related	**Clinical characteristics**
Age >65 years *Chronic kidney disease* *Diabetes mellitus* *Cancer or malignancy* *Previous CDI diagnosis*	*Hospital length of stay* *Nasogastric feeding tube* *Intensive Care Unit admission* *Gastrointestinal procedures*

Non-antibiotic medications can also cause distinct damage to human gut microbiome. First, gastric acid suppressant medications decrease microbial diversity in the gut by increasing gastrointestinal pH and inhibiting the growth of beneficial gut microbiota. Specifically, proton pump inhibitors interfere with microbial composition by restricting bacterial proton pumps, and are therefore suspected to be a greater risk for CDI than histamine 2 receptor antagonists in comparison.[23] Chemotherapeutic agents, nonsteroidal anti-inflammatory drugs, anti-ulcer medications, and corticosteroids are non-antibiotic medications that may also increase a patient's risk for CDI development.[38] Opioids have been investigated as a potential risk factor for CDI as well; however,

opioids were more strongly associated with the development of severe symptoms and complications of CDI, such as toxic megacolon, when taken around the time of the episode, as opposed to increasing the risk of developing initial infection.[11]

In addition to medications, host-related factors and clinical characteristics or interventions can play a role in the development of CDI. Healthcare-related exposures and factors that impact host immune response are most influential in these categories, including severe underlying illness, older age, and extended hospital or healthcare setting exposures, such as prolonged hospital length of stay or residency in a long-term care facility. Specifically, each additional day of a hospital stay increases CDI risk.[39] All of these risk factors should be considered by clinicians when evaluating a patient for possible to optimize diagnostics and timely treatment.

CLINICAL PRACTICE AND TREATMENT GUIDELINES

The primary clinical practice guidelines for CDI have been development and continually updated by IDSA/SHEA. Given the span of this sixteen-year retrospective study, it is important to review the specific differences in updated treatment guidelines over the study period. The practice guidelines for the treatment of CDI in adults published in 2010 can be seen summarized in Table 1.5.[39] Additionally, the updated guidelines, published in 2017, are summarized in Table 1.6.[35]

The overarching treatment approach has remained much the same over the past two decades. First, clinicians are recommended to discontinue therapy of any inciting antimicrobial agents, as this could affect the patient's risk of developing a recurrent infection. Evaluation should include patient age, 24-hour bowel movement count, white

blood cell count, and peak serum creatinine level, which will aid in determining the severity of the infection and guiding some treatment guidelines, such as candidate status for surgery. Patients should also be evaluated for dehydration and rehydrated with oral or intravenous rehydration therapies if needed. Finally, antibiotic therapy should be initiated following a positive *C. difficile* stool test or empirically in patients with a high probability of CDI based on their risk factors.[35]

Antibiotics are the mainstay therapy for CDI. In the 2017 guidelines, oral vancomycin or fidaxomicin are strongly recommended to treat the first episode of CDI (non-severe and severe). Oral metronidazole is weakly recommended in non-severe CDI if oral vancomycin or fidaxomicin are unavailable. Regardless of severity, treatment is recommended for ten days. An initial episode of fulminant CDI (CDI with shock, ileus, or megacolon) may be treated with oral vancomycin in combination with intravenous metronidazole. If oral metronidazole is used for the initial episode of CDI, oral vancomycin may be used to treat the first recurrence. Otherwise, a prolonged and tapered oral vancomycin regimen or fidaxomicin are recommended for first recurrence CDI. Subsequent recurrences may be treated with tapered and pulsed oral vancomycin (Vancomycin 125 mg PO 4 times daily for 10-14 days, then 2 times daily for 7 days, then daily for 7 days, and then every 2-3 days for 2-8 weeks), oral vancomycin followed by oral rifaximin, fidaxomicin, or fecal microbiota transplantation, although the expert panel recommends reservation of the fecal transplant for patients suffering at least two recurrences.

The major updates in the 2017 guidelines compared to the 2010 guidelines include the following: 1) metronidazole is no longer recommended first line, 2) fidaxomicin is now recommended as a first line option with vancomycin, 3) fecal transplant is recommended for patients with more than three CDI episodes, and 4) toxin tests are now emphasized as part of laboratory diagnostic algorithms. Metronidazole is no longer the recommended first line treatment.

Table 1.5. Practice guidelines for the treatment of adult CDI 2010.

Clinical appearance	**Treatment recommendation**
Initial episode, *mild to moderate (non-severe)*	Metronidazole 500 mg PO 3 times/day for 10-14 days
Initial episode, *severe*	Vancomycin 125 mg PO 4 times/day for 10-14 days
Initial episode, *severe complicated*[*]	Vancomycin 500 mg PO (or by rectum if ileus if present) 4 times/day and 500 mg in approx. 100 mL normal saline per rectum every 6 hours as retention enema ***with or without*** metronidazole intravenously every 8 hours
First recurrence[**]	Same regimen as patient's initial episode with stratification based on severity as stated above.
Subsequent recurrence(s)	Vancomycin therapy with tapered and/or pulse regimen
Patients with continued antimicrobial therapy for other underlying infections	No recommendations can be made for prevention of CDI in this population

[*]Consider colectomy for severely ill patients; monitor serum lactate levels and peripheral white blood cell count for decision making in surgery. Perform subtotal colectomy with preservation of the rectum.
[**]Do not use Metronidazole beyond first recurrence as long-term/chronic therapy to avoid potential neurotoxicity

Table 1.6. Practice guidelines for the treatment of adult CDI 2017 update.

Clinical appearance	**Treatment recommendation**
Initial episode, *mild to moderate (non-severe)*	Vancomycin 125 mg PO 4 times/day ***or*** fidaxomicin 200 mg twice/day for 10 days
Initial episode, *severe*[*]	A severe initial episode can be treated with the same dosage of vancomycin or fidaxomicin as an initial non-severe infection
Initial episode, *severe fulminant*[**]	Vancomycin 500 mg 4 times/day PO or NG tube. If ileus is present: rectal vancomycin enema (500 mg in 100 ml normal saline per rectum 4 times/day) Intravenous metronidazole 500 mg, 3 times daily can be added with oral or rectal vancomycin. Surgical intervention[†] may be required in patients w/ fulminant colitis, toxic megacolon, intestinal perforation, and/or necrotizing colitis
First recurrence	Prolonged taper and pulsed vancomycin regimen of 125 mg PO, 4 times/day for 10 to 14 days, 2 times/day for 7 days, once/day for 7 days, and lastly, once every 2 to 3 days for 2 to 8 weeks ***or*** fidaxomicin 200 mg PO, 2 times/day for 10 days *if vancomycin was used for the initial episode*.
Subsequent recurrence(s) [***]	Taper and pulsed vancomycin regimen as mentioned for the first recurrence, vancomycin 125 mg PO, 4 times/day for 10 days followed by rifaximin 400 mg PO, 3 times/day for 20 days, fidaxomicin 200 mg, 2 times/day for 10 days, ***OR*** fecal transplantation

[*]Severe infection is defined as a white blood cell count greater than 15,000 cells/microL, serum albumin less than 3 g/dL, and a serum creatinine level greater than 1.5 times the premorbid level

[**]Fulminant infection is defined as infection with the presence of hypotension, shock, ileus, or megacolon

[†]Subtotal colectomy with preservation of the rectum

[***]Bezlotoxumab has been recently approved for the management of recurrent CDI. Fecal transplantation has reported an 80% to 90% success rate in reducing the recurrence of CDI. Expert opinion suggests treating 3 total CDI occurrences with antibiotic therapy before attempting fecal transplantation for treatment.

Chapter 2: CDI and the Potential Relationship with Aging-Related Conditions

POST-CDI HEALTH OUTCOMES EXTEND BEYOND THE SHORT-TERM

CDI likely contributes to poor long-term outcomes and development of aging-related conditions. Given the substantial burden endured by CDI patients in the short-term, it is likely that these patients may be at risk for poor long-term outcomes as well. The biological mechanism for this relationship may be due to the significant impact CDI and antibiotic therapy place on the human gut microbiota. The gut microbiota play an important role in maintaining human health (i.e., healthspan), including energy and nutrient extraction, host immune system modulation, and protection against pathogens.[6] CDI pathogenesis has been linked to a disruption in the normal gut microbiota (i.e., dysbiosis), predominantly following antibiotic exposure. In addition, antibiotics are the mainstay therapy for CDI and prior studies have found that recovery of the microbiome post-antibiotic use is slow and that some patients never fully restore microbiome diversity.[40] In the short-term, this increases the risk for CDI recurrence; however, long-term dysbiosis could increase the risk for several other health conditions. Microbiome dysbiosis has been associated with systemic inflammation, a multitude of aging-related conditions, and frailty, all of which pose a significant burden on the health of patients and the health care system.[41] When the microbiome becomes disrupted due to antibiotic exposure, CDI, or age-related changes, the functional benefits may be altered. In a normal healthy individual, once the stressor is removed, the microbiome is able to fully

recover; however, in some individuals, these stressors may permanently deplete essential commensal bacteria, preventing full microbiome recovery.[42,43] This can ultimately lead to poorer health outcomes and decreased healthspan and lifespan, particularly in an elderly and aging population. Specifically, studies have found that gut dysbiosis can influence the development of several diseases and aging-related conditions.[44]

Unhealthy aging as a result of CDI poses a significant problem to patients and the healthcare system. Increases in aging-related health problems due to CDI potentially pose a significant burden to the healthcare system, especially as the population ages. Age-related health problems, including bone fractures and dementia, contribute to frailty, which is characterized by declines in physiologic reserve and function, resulting in increased risk of adverse health outcomes.[45] The prevalence of frailty is estimated to be at least 10% among community-dwelling U.S. adults, and increases with age.[46] The associated costs of frailty were estimated to be more than $18 billion in 2000, with a continued increase over the next two decades.[47] Thus, in the setting of an aging population and growing incidence of CDI, an increasingly frail older population will have major implications for the demand for health care services, including hospital usage, home care, and long-term care.

Healthspan and lifespan effects of CDI could inform new drug development and clinical practice. Prior clinical trials have identified patient-specific factors that increase the risk for mortality and recurrent CDI, including advanced age, immunosuppression, concomitant use of non-CDI antimicrobial therapy or gastric-acid suppressing drugs, long hospital stays, and severity of illness.[48,49] Given the association between dysbiosis and

aging-related conditions, it is possible that similar factors might affect risk for development of aging-related conditions; however, it is unclear the extent to which these factors impact these conditions, nor whether certain therapies can mitigate risk. This represents a significant knowledge gap in the care for patients with CDI. While certain patient factors may not be modifiable (e.g., age), other factors like treatment decisions and access to care could be optimized to improve CDI health outcomes and ultimately promote healthy aging. For example, fidaxomicin has a narrower spectrum of activity compared to vancomycin, with high activity against *C. difficile* while preserving more of the normal gut microbiota. In addition, alteration of the gut microbiota in the setting of CDI and aging-related diseases has prompted interest in the use of prebiotics, probiotics, and fecal microbiota transplantation (FMT). Prebiotics support the nourishment of the normal gut microbiota, while probiotics and FMT aim to restore its microbial diversity and structure. Prior studies documented increased diversity and restoration of specific bacterial taxa and important metabolites following FMT in patients with *C. difficile* infection,[50,51] while safely improving patient outcomes.[52] More recently, rationally designed combinations of microbes (i.e., Ecobiotics) are being developed to target known microbial deficiencies. Other therapies that target the immune response could also serve as a potential option during CDI to promote positive long-term outcomes. Immune response to *C. difficile* is a major determinant of health outcomes among patients with CDI;[53] therefore, immunomodulatory therapies, such as statins, immune globulins, and monoclonal antibodies may play a role in reducing the risk of CDI recurrence. Our

population-based study will serve to inform treatment decisions to potentially improve healthspan and lifespan among patients who develop CDI.

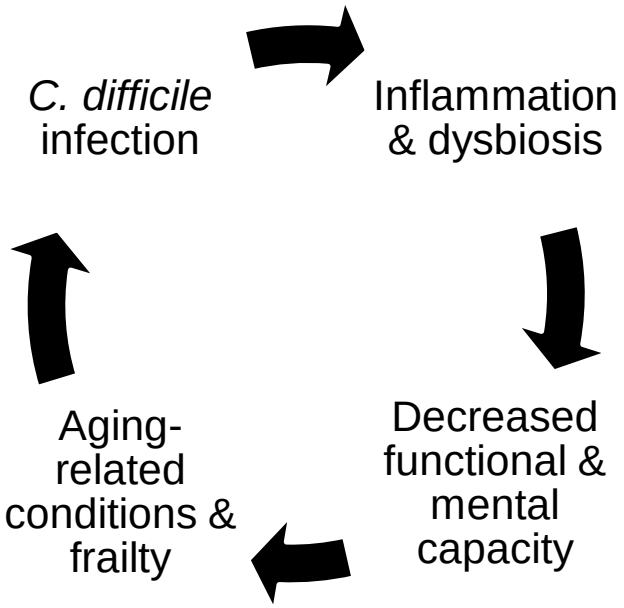
GUT MICROBIOME DYSBIOSIS AND AGING

Gastrointestinal microbiome dysbiosis has been linked to a number of aging-related chronic conditions, including frailty, cancer, and cardiovascular, metabolic, and neurological diseases. These conditions place a major burden on patients, caregivers, and the healthcare system, including increasing demand for health care services (e.g., hospital and long-term care). **Given the strong link between dysbiosis and CDI, as well as dysbiosis and other aging-related conditions, we hypothesize that CDI will accelerate the development of aging-related conditions.** Population-based analysis of this relationship will ultimately help inform prospective clinical studies to validate this association, as well as determine the underlying mechanisms and inform preventive interventions.

The scientific rationale for studying the effects of CDI on healthy aging stems from the strong biological connections mediated by gut microbiome dysbiosis and inflammation (Figure 2.1), as well as prior supporting epidemiological studies. The complexity of the human immune system and the gut microbiome aids in promoting healthy aging and, in turn, prevention of disease. The immune system comprises innate and adaptive properties which, over time, recognize the commensal bacteria residing in our bodies, forming a symbiotic alliance. Although this relationship ultimately protects the host from most harm, disruption of the normal gut microbiota can predispose to many

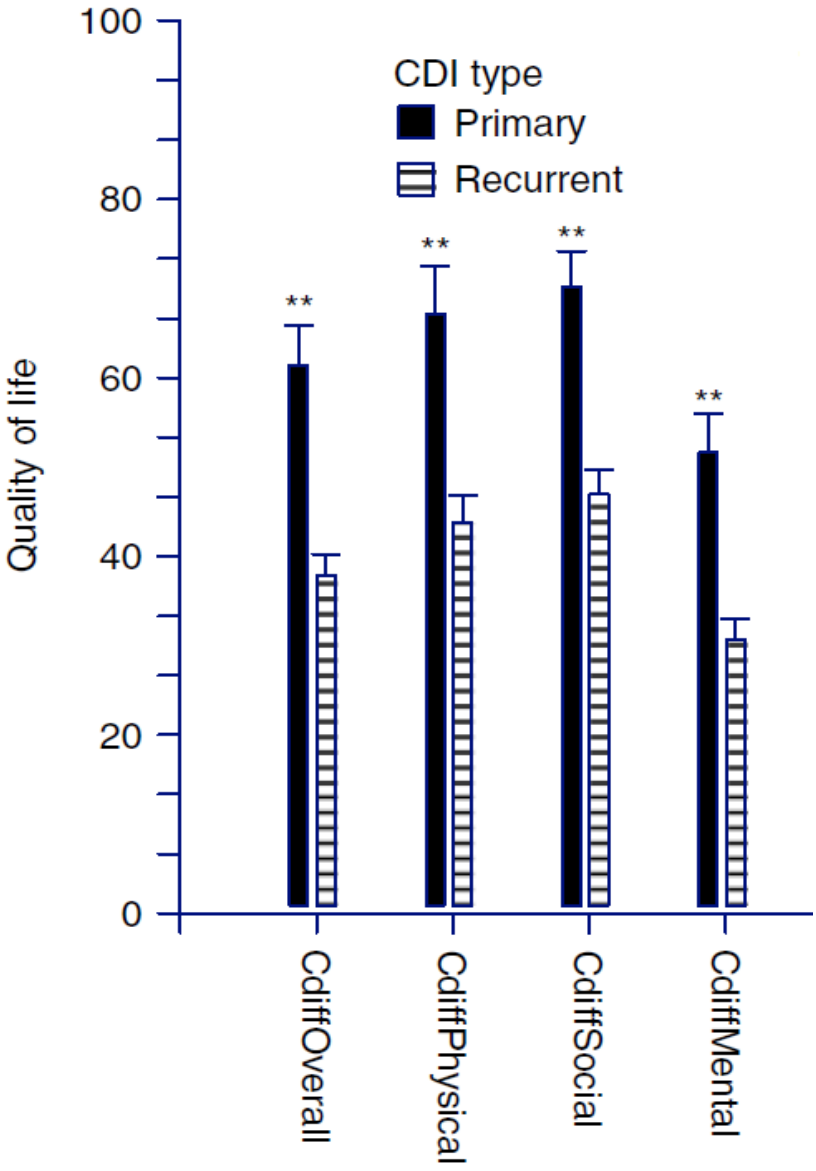
diseases. For example, recovery of the microbiome post-antibiotics can take up to 90 days, with some original taxa not fully recovering to its original composition,[40,42,43] suggesting that a combination of both CDI and antibiotic therapy could create an even further devastating, and potentially irreversible effect, on the gut microbiome composition. In an aging population, changes to the gut microbiota can increase the risk for a number of chronic conditions, including cardiovascular disease, metabolic disease, and neurological disorders like Alzheimer's Disease and Parkinson's Disease.[41] In addition, those experiencing a loss of microbial diversity in the distinct core groups of bacterial taxa has been associated with reduced cognitive performance and increased frailty.[54]

Figure 2.1. Relationship between CDI and aging.



Our research team has generated substantial preliminary data for the proposed project. We found that the national incidence of CDI among veterans more than tripled between 2003 and 2013 (1.6 vs. 5.1 cases/10,000 population). CDI patients were older (median age 67 years) and had multiple other comorbidities. We also noted a high rate of 30-day mortality (21%) and CDI recurrence (17%) in this population.[15] We have also described the shift from hospital- to community-onset CDI,[55] and created a prediction model for CDI recurrence among veterans.[56] Most recently, we found that hospitalized patients with CDI frequently required a higher level of medical care residence (e.g., nursing home) at discharge compared to non-CDI patients.[34] While we couldn't ascertain the reason for this association, we hypothesize that this could be due to the poor physical and mental functioning associated with CDI. CDI patients, especially those with recurrent infection, have poor quality of life scores in the short-term, as indicated by the Cdiff32 survey (Figure 2.2).[33] Because of the biological plausibility and preliminary studies, we propose that CDI patients will have poorer health at follow-up compared to controls and that certain CDI and treatment characteristics will predict healthy aging outcomes among CDI patients. This will be the first study to evaluate the long-term impact of CDI on health outcomes.

Figure 2.2. Mean CDI quality of life scores.



KNOWLEDGE GAPS

To our knowledge, no studies have evaluated the long-term effects of CDI on healthy aging, nor identified factors that promote healthy aging in this population. To inform this knowledge gap, we propose a series of study aims that seek to address the **central hypothesis** that CDI significantly impacts healthy aging, likely due to its influence on the gut microbiome and inflammation, and that certain CDI and patient characteristics will be associated with better outcomes among patients who develop CDI. Specifically, our **overall objective** is to test if CDI impacts the development of aging-related conditions, frailty, and longevity in a national, retrospective cohort of veterans with longitudinal follow-up over 16 years.

The study is **innovative** because it will be the first study to assess the long-term impact of CDI on healthy aging. The study will inform predictors of long-term outcomes of CDI and inform potential interventions for healthy aging. The proposed research is expected to have a **positive impact** on human health by promoting the importance of CDI prevention and giving consideration to predictors that will guide future treatments to decrease the healthcare burden of older adults. Our team plans to use the results of this study to support a prospective clinical study of CDI patients to validate study findings, determine the biological basis for such associations, and guide future treatment decisions for patients with CDI.

We utilized the largest population to date to study the association between CDI and these important outcomes. We assessed approximately 31,513 CDI patients and 81,293 controls within the Veterans Health Administration (VHA) over a 16-year period.

Use of the VHA comprehensive electronic medical record system allowed us to capture inpatient and outpatient diagnoses and to follow patients longitudinally, minimizing the risk for misclassification. The size of the population also allowed us to run subgroup analyses on underrepresented populations, such as women, to enhance generalizability. We used robust statistical analyses that reduced the impact of confounding. Importantly, our team was able to expertly assess and interpret the clinical significance of a statistically significant effect size, given the large sample size.

Chapter 3: Specific Aim and Hypotheses

SPECIFIC AIM 1: DESCRIBE THE SHORT-TERM HEALTH OUTCOMES OF CDI IN A NATIONAL RETROSPECTIVE VETERAN COHORT

Hypothesis 1.1: CDI patients will experience earlier mortality over 1-, 3-, and 12-month follow-up periods compared to non-CDI controls

Hypothesis 1.2: CDI patients will experience more aging-related conditions over 1-, 3-, and 12-month follow-up periods compared to non-CDI controls

Hypothesis 1.3: CDI patients will experience more frailty-associated diagnoses over 1-, 3-, and 12-month follow-up periods compared to non-CDI controls

SPECIFIC AIM 2: DEFINE THE LONG-TERM IMPACT OF CDI ON HEALTHY AGING IN A NATIONAL RETROSPECTIVE VETERAN COHORT

Hypothesis 2.1: CDI patients will experience earlier mortality over a 10-year follow-up period compared to non-CDI controls

Hypothesis 2.2: CDI patients will experience more aging-related conditions over a 10-year follow-up period compared to non-CDI controls

Hypothesis 2.3: CDI patients will experience more frailty-associated diagnoses over a 10-year follow-up period compared to non-CDI controls

Chapter 4: Research Strategy

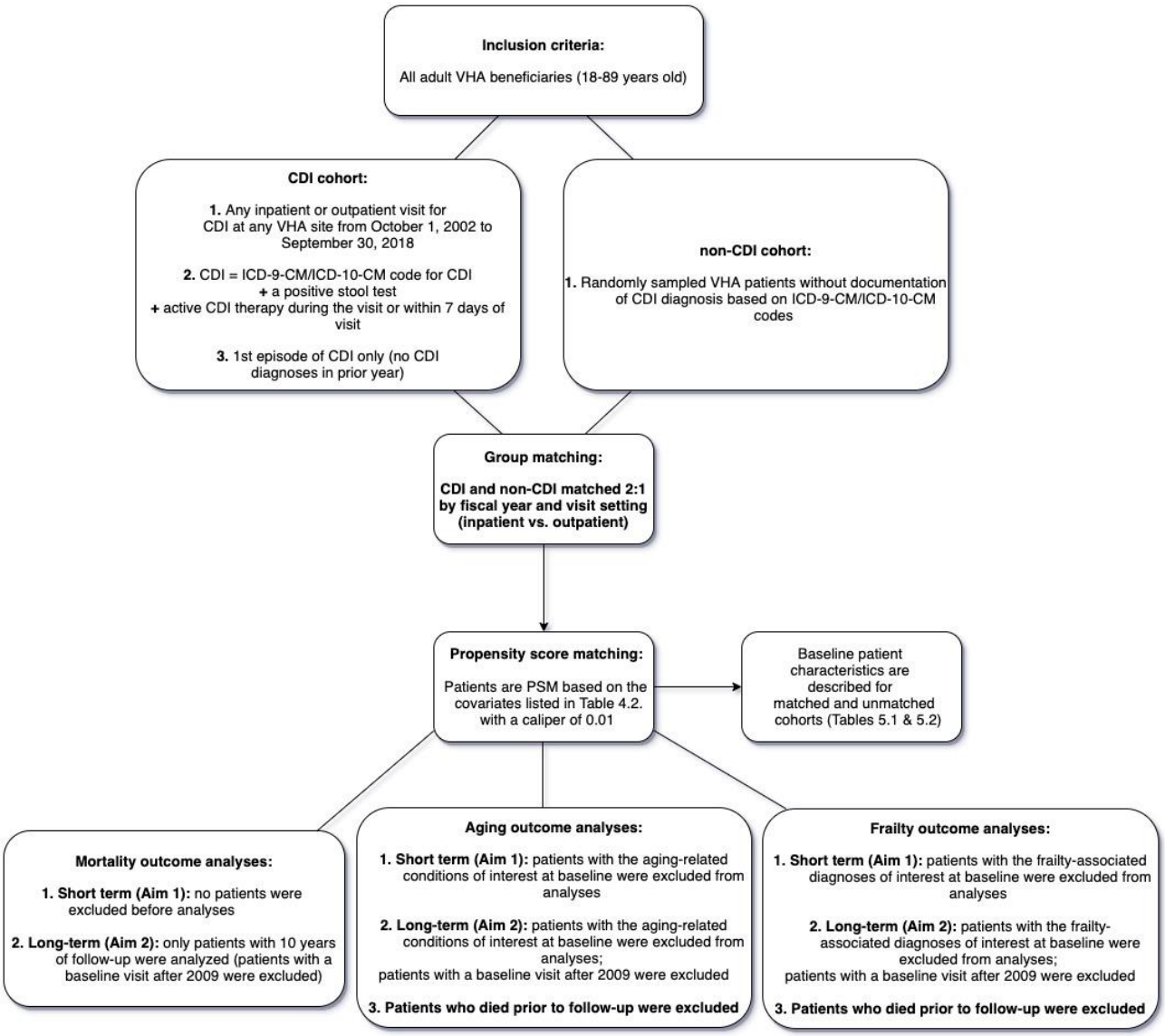
RESEARCH DESIGN

This was a retrospective cohort study of all patients receiving care at any of the approximately 171 VHA hospitals and 1,283 VHA clinics in the U.S. Data were obtained from the VA Informatics and Computing Infrastructure, which includes administrative, clinical, laboratory, and pharmacy data repositories which are linked using unique patient identifiers. Specifically, the team used four national VA data sources: the VA Medical SAS Datasets (both inpatient and outpatient), the VA Vital Status File, the VA Decision Support System, and the VHA Annual Enrollment Files. The VA Medical SAS Inpatient Dataset includes patient demographics, diagnoses, procedures, hospital length of stay, and discharge status. The VA Medical SAS Outpatient Dataset includes patient demographics, diagnoses, and procedures. The VA Vital Status File contains date of birth and death, and gender for each veteran. The VA DSS integrates data from clinical and financial systems to create National Data Extracts (NDEs). NDEs include laboratory results and both inpatient and outpatient pharmacy records. Finally, the VHA Annual Enrollment Files contain eligibility information that was used to create priority groups. All data collection and analyses were performed at the South Texas Veterans Health Care System, Audie L. Murphy VA Hospital, San Antonio, TX.

Study Population

All adult VHA beneficiaries (18-89 years old) were eligible for study inclusion. The CDI cohort included adult patients who had any inpatient or outpatient visit for CDI at the VA from October 1, 2002 to September 30, 2018 (cohort inclusion period). Patients eligible for the full 10-year outcome analysis were patients with CDI between October 1, 2002 and September 30, 2008. CDI was defined as an ICD-9-CM or ICD-10 code for CDI (008.45 and A04.72, respectively), plus a positive stool test (e.g., glutamate dehydrogenase, toxin enzyme immunoassay, polymerase chain reaction), and active CDI therapy during the visit or within 7 days of the visit during the cohort inclusion period. To limit survivor bias, we limited the cohort to first CDI episodes only by excluding patients with an ICD-9-CM code for CDI in the year prior to cohort inclusion. A control group was created by randomly sampling VHA patients without an ICD-9-CM or ICD-10-CM code for CDI at any time during the study period, group matching to the CDI cohort 2:1 based on fiscal year and visit setting (inpatient vs. outpatient).

Figure 4.1. Patient cohort, matching, and analysis algorithm.



Data Collection

Data extraction and variable creation were conducted using SAS Version 9.4 (SAS Institute, Cary, NC, USA). Propensity score matching was performed using STATA 14 (StataCorp, College Station, TX, USA). All other data and statistical analyses were conducted using JMP 14 (SAS Institute, Cary, NC, USA). All variables were presented descriptively, with continuous variables presented as means, standard deviations, medians, and interquartile ranges as appropriate. Categorical variables were presented as the number and percentage of subjects in each category. For baseline characteristics (e.g., sex, race, ethnicity, priority group), we included a "missing" category. Other variables that were absent from the medical chart (e.g., comorbidities, medications) were assumed to have not occurred. For all analyses, we reduced the risk for type I error by setting the threshold for statistical significance as $p<0.0001$ for both bivariable and multivariable analyses.

Study dependent variables

Study dependent variables included all-cause mortality, aging-related conditions, and frailty-associated diagnoses (Table 4.1). The primary outcome was all-cause mortality assessed as a dichotomous variable at specific time points (1 month, 3 months, 12 months, and 10 years) as well as a continuous variable for survival analysis. Time to death was defined as the date of death minus the date of cohort inclusion (date of CDI diagnosis or matching control visit) during the cohort inclusion period. Secondary outcomes included aging-related conditions and frailty-associated diagnoses, which were

assessed as dichotomous variables at specific time points (1 month, 3 months, 12 months, and 10 years). Aging-related conditions included cardiovascular disease (myocardial infarction or stroke), cancer, and neurodegenerative diseases (dementia, Alzheimer's diseases, Parkinson's disease). These diagnoses were chosen due to their association with age and gut microbiome dysbiosis.[27] Frailty-associated diagnoses included coagulopathy, involuntary weight loss, fluid & electrolyte imbalance, anemia, and fall or fracture. The diagnoses were chosen based on literature review and expert opinion, as well as supporting evidence from investigators that support the association between frailty-related diagnoses and hospital readmissions.[45] Additionally, we compared the validated VHA Frailty Index used in VA hospitals and clinics to determine frailty and fall risk in elderly patients. To ensure temporality of the association between CDI and aging- and frailty-related health outcomes, we excluded patients who had any of the outcome variables listed in Table 4.1 at the time of cohort inclusion or within one year prior to cohort inclusion.

Table 4.1. Summary of study dependent variables.

Dependent variable	Definition
All-cause mortality	Death as indicated in the VA Vital Status File
Aging-related conditions	Indicated by ICD-9 or ICD-10 code below
Cardiovascular disease	410, 412, 430-438 (ICD-9) or I21, I63.0-I63.9 (ICD-10)
Cancer	140-172, 174-208 (ICD-9) or C&D codes (ICD-10)
Neurodegenerative diseases	290, 294, 331-2 (ICD-9) or G20, G30-1, F01-3 (ICD-10)
Frailty-associated diagnoses	Indicated by ICD-9 or ICD-10 code below
Coagulopathy	286.0-286.9 (ICD-9) or D65-D69 (ICD-10)
Involuntary weight loss	783.21 (ICD-9) or R63.4 (ICD-10)
Fluid & electrolyte imbalance	276.9 (ICD-9) or E87 (ICD-10)
Anemia	280.0-285.9 (ICD-9) or D60-D64 (ICD-10)
Falls	V15.88 (ICD-9) or Z91.81 (ICD-10)
Fracture	800.0-829.9 (ICD-9) or S02, S22, S32, M48 (ICD-10)

Study control variables

A summary of all independent variables is provided in Table 4.2. In brief, patient demographics, including sex, race, and Hispanic ethnicity were defined as the most frequent reporting of each over the study period to ensure accuracy. Geographic region was defined by the VA Integrated Service Network (VISN) in which the patient was seen for their study inclusion visit. VHA priority group was included as a marker of socioeconomic and disability status. Healthcare exposures in the prior year included inpatient and outpatient visits to the VA, chronic dialysis, and long-term care facility residence. These variables aid in determining patient acuity and healthy-user bias in each cohort. Charlson comorbidities were collected in the year prior to study inclusion and during follow-up as defined by Deyo, et al.[57] Selim psychiatric comorbidities and other relevant diagnoses were also collected, as defined by ICD-9-CM or ICD-10 codes. We also evaluated medications likely to increase the risk for CDI, including antibiotics,

gastric acid suppressants, opioids, motility agents, and cancer chemotherapy. Given the long follow-up period, there are several factors that could impact risk for mortality or development of aging-related conditions that should were controlled for in our analysis. We evaluated healthcare exposures, comorbidities, and medications over the course of the follow-up period. In addition, we included several factors that could impact outcomes, including concomitant non-CDI antibiotic use, concomitant infections, and severity indicators (Table 4.3). Community-onset CDI (CO-CDI) was defined based upon the presence of CDI therapy initiated in the outpatient setting or on days 1 or 2 of hospitalization. Community-onset, healthcare facility-associated CDI (CO-HCFA-CDI) was defined the same way, with the addition of a hospitalization in the prior 90 days. Lastly, healthcare facility-onset CDI was defined as CDI therapy beginning on day 3 or later of hospitalization. We also captured number of CDI episodes over the study period to determine a "dose-response" relationship between CDI and development of aging- and frailty-related conditions.

Table 4.2. Study control variables

Propensity score covariates	Regression & Cox model covariates
Demographics:	
Age, sex, race, Hispanic ethnicity	**Exposures during 10-year follow-up:**
Fiscal year	Inpatient & outpatient visits
Geographic region (VISN)	Chronic dialysis
VHA priority group & copay status	Long-term care facility
Exposures in prior year:	**Medications during 10-year follow-up:**
Inpatient & outpatient visits	Antibiotics
Chronic dialysis	Gastric acid suppressants
Long-term care facility	Laxatives or anti-diarrheals
Medications in prior 90 days:	Narcotics
Antibiotics	Cancer chemotherapy
Gastric acid suppressants	**Charlson comorbidities in 10-year follow-up**
Laxatives or anti-diarrheals	**Selim comorbidities in 10-year follow-up**
Narcotics	**Severity indicators during encounter**
Cancer chemotherapy	**Concomitant infections during encounter**
Charlson comorbidities in prior year	**CDI antibiotic & adjunctive therapies**
Selim comorbidities in prior year	**Number of CDI episodes**
Other important comorbidities	**CDI type (community- vs. hospital-onset)**
VHA frailty index	

Table 4.3. Indicators of severe CDI infection.

CDI severity indicator	Clinical definition
White blood cell count	$>15\times10^9$/L
Serum creatinine	≥1.5 mg/dL
Albumin	<2.5mg/dL
Sepsis/septicemia	ICD-9-CM: 020.2, 038.0-038.9, 995.91, 995.92 ICD-10: R65.2X, A41.X
Shock/septic shock	ICD-9-CM: 639.5, 785.52, 785.59 ICD-10: R57.0, R57.1, R57.8, R57.9, R65.21
Prolonged ileus	ICD-9-CM: 560.1 ICD-10: K56.0, K56.4, K56.6X, K56.7
Megacolon	ICD-9-CM: 558.2, 564.7 ICD-10: K52.1, K59.31, K59.30

PROPENSITY SCORE MATCHING AND CONDITIONAL LOGISTIC REGRESSION

CDI and control groups were propensity score-matched based on characteristics at cohort inclusion (Table 4.2). We estimated the probability of patients experiencing CDI using a logistic regression model with CDI as the dependent variable and the following covariates: patient demographics, comorbidities and exposures in prior year, and medications in the prior 90 days. For aging and frailty analyses, patients who experienced the outcome of interest (i.e., those with pre-existing conditions) and those who died prior to the follow-up period were excluded from the sample. We then matched CDI patients to non-CDI controls 1:1 within a propensity score maximum caliper of 0.01. This small caliper aimed to tightly match cohorts, while limiting the sample size such that the analyses would not be substantially over-powered. Following propensity score matching, a series of multivariable logistic regression models were used to compare dichotomized study dependent variables between CDI and non-CDI control groups at various time points (1 month, 3 months, 12 months, and 10 years) using the covariates in Table 4.2. Dependent variables were also defined as continuous variables for time-to-event analyses. The variables were then be assessed using a Cox proportional hazard model with covariates as described above. For each model, independent variables were considered significant predictors of each dependent variable if $p<0.0001$. Data were presented as adjusted odds ratios and 99% confidence intervals.

SUBGROUP ANALYSES

Given that the VHA population is mostly male (97%), we conducted a subgroup analysis in females only. For this analysis, we repeated the propensity score matching and conditional logistic regression modeling techniques as described above in female patients

only. We also performed subgroup analyses on patients with community-onset CDI (CO-HCFA-CDI and CA-CDI), as CDI type could substantially impact survivor bias.

Power and Sample Size

In our prior work, we built a national cohort of veterans that included 26,149 CDI patients and 59,309 control patients from fiscal year 2003 to 2014. In this study, we extended the cohort inclusion dates to fiscal year 2018. Given this extension, we have 31,513 CDI patients and 81,293 controls. For the analyses that will require 10-year follow-up, we have 8,521 CDI patients and 21,302 controls available for complete follow-up. We conducted a power calculation for our primary outcome of all-cause 90-day mortality. From preliminary analyses in the unmatched cohorts, approximately 21.7% of CDI patients and 2.2% of controls experienced 90-day mortality. Using a p-value of 0.0001, we will achieve near 100% power for this comparison; however, the sample size is expected to decrease following matching. For 10-year mortality, we approximate that 72.8% of CDI patients and 29.0% of controls will experience mortality. Using a p-value of 0.0001, we will achieve near 100% power for this comparison though similar sample size reductions will be seen post-matching. We acknowledge that this large sample size might result in statistically significant differences between groups even with a small effect size. Because of this, we reduced the p-value cutoff for statistical significance and used a small caliper (0.01) for propensity score matching.

Responsible and Ethical Conduct

The research conducted in this study does not contain human or animal subjects and only involves work with de-identified secondary sources of human medical information. This retrospective cohort study was conducted in accordance with the ethics, regulations, and governing medical practice in accordance with current, acceptable techniques and expertise in the United States. The research protocol was dually reviewed and approved by the Institutional Review Boards (IRBs) at the South Texas Veterans Health Care System and the University of Texas Health San Antonio campus (approval # HSC20130473H), per current practice as part of the dual-campus research agreement.

Subject informed consent is not applicable to this retrospective cohort study and was therefore allotted an IRB waiver for the informed consent requirement. Additionally, this research involves the use of existing data only, and no healthcare providers or patients were contacted at any point during the study period. Data used for this research is currently maintained on VA research servers in directories with limited access behind the VA firewall system, making a data breach unlikely to occur. Any research personnel with access to this data must maintain up-to-date training regarding knowledge and practice of stable security processes. Data collection and analysis were performed only by those with VHA appointments, therefore, only those with qualified VHA access would and will have any access to patient identifying information for the purpose of merging data. No data in this research was reported at an individual level for enhanced protection of patient information.

Chapter 5: Results

BASELINE CHARACTERISTICS

A total of 40,643 patients met inclusion for the CDI cohort based on the presence of a CDI diagnosis code and positive stool test. From this cohort, 446 were excluded for a diagnosis of CDI in the previous year and 8,684 were excluded for lack of documented CDI active antibiotic therapy, leaving 31,513 CDI patients for analyses. A total of 81,293 patients met the study inclusion criteria for non-CDI controls, for a total of 112,806 patients in the combined CDI and control cohorts. Baseline characteristics for this unmatched study population are summarized in Table 5.1.

CDI patients were predominantly elderly (median age 67 years), white (75.3%) males (95.4%) with a median (IQR) Charlson comorbidity score of 2 (1-4). The most common Charlson comorbidities for CDI patients in the prior year included: diabetes without (37.4%) or with (17.1%) complications, COPD (34.7%), cancer (25.3%), and renal disease (23.4%). Other comorbidities were also prevalent among CDI patients, including hypertension (72.0%), IBD (29.4%), GERD (26.4%), and depression (24.4%). CDI patients were also commonly exposed to medications known to impact CDI development risk in the 90 days preceding the index CDI diagnosis, including antibiotics (52.8%) and gastric acid suppressants (53.8%).

In these unmatched cohorts, CDI and control patients significantly differed in nearly all variables assessed. CDI patients more frequently had healthcare exposures

(outpatient/inpatient visits, dialysis, LTCF residence), medications exposures in the previous 90 days, and comorbidities documented in the previous year (Table 5.1).

Table 5.1. Patient baseline characteristics of unmatched cohorts

	Total N (%) (n=112,806)	**CDI Cohort N (%) (n=31,513)**	**Non-CDI Cohort N (%) (n=81,293)**	**P-value**
Fiscal year				0.1350
2003	3476 (3.1%)	994 (3.4%)	2482 (3.1%)	
2004	4756 (4.2%)	1384 (4.4%)	3372 (4.2%)	
2005	5389 (4.8%)	1557 (4.9%)	3832 (4.7%)	
2006	5435 (4.8%)	1548 (4.9%)	3887 (4.8%)	
2007	5284 (4.7%)	1499 (4.8%)	3785 (4.7%)	
2008	5483 (4.9%)	1539 (4.9%)	3944 (4.9%)	
2009	5383 (4.8%)	1517 (4.8%)	3866 (4.8%)	
2010	6421 (5.7%)	1775 (5.6%)	4646 (5.7%)	
2011	9627 (8.5%)	2715 (8.6%)	6912 (8.5%)	
2012	11314 (10.0%)	3132 (9.9%)	8182(10.1%)	
2013	13213 (11.7%)	3683 (11.7%)	9530(11.7%)	
2014	12785 (11.3%)	3500 (11.1%)	9285(11.4%)	
2015	11893 (10.5%)	3321(10.5%)	8572(10.5%)	
2016	549 (0.5%)	133 (0.4%)	416 (0.5%)	
2017	1381 (1.2%)	347 (1.1%)	1034 (1.3%)	
2018	10417 (9.2%)	2869 (9.1%)	7548 (9.3%)	
Age*	63 (54-71)	67 (60-78)	61 (53-69)	<0.0001
Sex				<0.0001
Female	6811 (6.1%)	1437 (4.6%)	5374 (6.6%)	
Male	105995 (93.9%)	30076(95.4%)	75919 (93.4%)	
Race				<0.0001
White	80308 (71.2%)	23729(75.3%)	56579 (69.6%)	
Black	25429 (22.5%)	5143 (16.3%)	20286 (24.9%)	
Other	1884 (1.7%)	502 (1.6%)	1382 (1.7%)	
Missing	5185 (4.6%)	2139 (6.8%)	3046 (3.8%)	

Table 5.1, *cont.*

Ethnicity				<0.0001
Hispanic	5666 (5.1%)	1366 (4.3%)	4400 (5.4%)	
Not Hispanic	106136 (94.1%)	29366 (93.2%)	76770 (94.4%)	
Missing	904 (0.8%)	781 (2.5%)	123 (0.2%)	
Setting				<0.0001
Inpatient	100208 (88.8%)	28235 (89.6%)	71973 (88.5%)	
Outpatient	12598 (11.2%)	3278 (10.4%)	9320 (11.5%)	
VHA priority group				<0.0001
Group 1	18331 (16.3%)	4228 (13.4%)	14103 (12.5%)	
Group 2	4649 (4.1%)	1167 (3.7%)	3482 (3.1%)	
Group 3	7153 (6.3%)	1938 (6.2%)	5215 (4.6%)	
Group 4	1923 (1.7%)	748 (2.4%)	1175 (1.0%)	
Group 5	31500 (27.9%)	9460 (30.0%)	22040 (19.5%)	
Group 6	1584 (1.4%)	509 (1.6%)	1075 (0.9%)	
Group 7	2618 (2.3%)	948 (3.0%)	1670 (1.5%)	
Group 8	3028 (2.7%)	1081 (3.4%)	1947 (1.7%)	
Geographic region (VISN)**				<0.0001
VISN 1	6088 (5.4%)	2645 (8.4%)	3443 (4.2%)	
VISN 2	7743 (6.9%)	2323 (7.4%)	5420 (6.7%)	
VISN 4	4524 (4.0%)	1212 (3.8%)	3312 (4.1%)	
VISN 5	4986 (4.4%)	1464 (4.6%)	3522 (4.3%)	
VISN 6	5245 (4.7%)	1140 (3.6%)	4105 (5.1%)	
VISN 7	6085 (5.4%)	1605 (5.1%)	4480 (5.5%)	
VISN 8	10586 (9.4%)	2936 (9.3%)	7650 (9.4%)	
VISN 9	5347 (4.7%)	1385 (4.4%)	3962 (4.9%)	
VISN 10	8223 (7.3%)	1482 (4.7%)	6741 (8.3%)	
VISN 12	6956 (6.2%)	1987 (6.3%)	4969 (6.1%)	
VISN 15	6139 (5.4%)	2415 (7.7%)	3724 (4.6%)	
VISN 16	6648 (5.9%)	1461 (4.6%)	5187 (6.4%)	
VISN 17	5535 (4.9%)	1201 (3.8%)	4334 (5.3%)	
VISN 19	4810 (4.3%)	1572 (4.9%)	3238 (3.9%)	
VISN 20	3939 (3.5%)	884 (2.8%)	3055 (3.8%)	
VISN 21	4812 (4.3%)	1382 (4.4%)	3430 (4.2%)	
VISN 22	9616 (8.5%)	2994 (9.5%)	6622 (8.1%)	
VISN 23	5518 (4.9%)	1422 (4.5%)	4096 (5.0%)	
Exposures in prior year				
*Inpatient visits**	0 (0-1)	1 (0-2)	0 (0-1)	<0.0001
*Outpatient visits**	26 (13-48)	28 (14-49)	26 (13-47)	<0.0001
Chronic Dialysis	2797 (2.5%)	1423 (4.5%)	1374 (1.7%)	<0.0001
Long-term care facility	6301 (5.6%)	4150 (13.2%)	2151 (2.7%)	<0.0001

Table 5.1, *cont.*

Medications in prior 90 days				
Antibiotics	35884 (31.8%)	16632 (52.8%)	19252 (23.7%)	<0.0001
Gastric acid suppressants	47411 (42.0%)	16938(53.8%)	30473 (37.5%)	<0.0001
Laxatives	11524 (10.2%)	5242 (16.6%)	6282 (7.7%)	<0.0001
Anti-diarrheals	3497 (3.1%)	2097 (6.7%)	1400 (1.7%)	<0.0001
Opioids	36633 (32.5%)	13595(43.1%)	23038 (28.3%)	<0.0001
Cancer chemotherapy	4262 (3.8%)	1799(5.7%)	2463 (3.0%)	<0.0001
Charlson comorbidities in prior year				
Myocardial infarction	5647 (5.0%)	2547 (8.1%)	3100 (3.8%)	<0.0001
Congestive heart failure	16607 (17.7%)	6913 (21.9%)	9694 (11.9%)	<0.0001
Peripheral vascular disease	15512 (13.8%)	6193 (19.7%)	9319 (11.5%)	<0.0001
Cerebrovascular disease	13520 (11.9%)	5330 (16.9%)	8190 (10.1%)	<0.0001
Dementia	3157 (2.8%)	1628 (5.2%)	1529 (1.9%)	<0.0001
Chronic pulmonary disease	31339 (27.8%)	10946(34.7%)	20393 (25.1%)	<0.0001
Rheumatic disease	2370 (2.1%)	892 (2.8%)	1478 (1.8%)	<0.0001
Peptic ulcer disease	2504 (2.2%)	1112 (3.5%)	1392 (1.7%)	<0.0001
Mild liver disease	10375 (9.2%)	3647 (11.6%)	6728 (8.3%)	<0.0001
Diabetes w/o complications	40299 (35.7%)	11785(37.0%)	28514 (35.1%)	<0.0001
Diabetes w/ complications	16120 (14.3%)	5393 (17.1%)	10727 (13.2%)	<0.0001
Hemiplegia or paraplegia	4012 (3.6%)	1559 (4.9%)	2453 (3.0%)	<0.0001
Renal disease	16451 (14.6%)	7359 (23.4%)	9092 (11.2%)	<0.0001
Cancer	18782 (16.7%)	7984 (25.3%)	10798 (13.3%)	<0.0001
Cancer metastasis	3008 (2.7%)	1871 (5.9%)	1137 (1.4%)	<0.0001
Moderate/severe liver Disease	1522 (1.4%)	799 (2.5%)	723 (0.9%)	<0.0001
HIV/AIDS	1520 (1.3%)	513 (1.6%)	1007 (1.2%)	<0.0001
Charlson comorbidity score*	1 (0-3)	2 (1-4)	1 (0-2)	<0.0001

Table 5.1, *cont.*

Selim comorbidities in prior year				
Schizophrenia	7822 (6.9%)	1153 (3.7%)	6669 (8.2%)	<0.0001
Depression	31701 (28.1%)	8017 (25.4%)	23684 (29.1%)	<0.0001
Bipolar disorder	17208 (15.3%)	3226 (10.2%)	13982 (17.2%)	<0.0001
Anxiety disorder	7071 (6.3%)	1841 (5.8%)	5230 (6.4%)	0.0002
Post-traumatic stress disorder	21842 (19.4%)	4062 (12.9%)	17780 (21.9%)	<0.0001
Alcohol abuse	3158 (2.8%)	1074 (3.4%)	2084 (2.6%)	<0.0001
Other comorbidities in prior year				
Hypertension	74544 (66.1%)	22698 (72.0%)	51846 (63.8%)	<0.0001
Dyslipidemia	6349 (5.6%)	1818 (5.8%)	4531 (5.6%)	0.2025
Obesity	23460 (20.8%)	5579 (17.7%)	17881 (22.0%)	<0.0001
GERD	27099 (24.0%)	8332 (26.4%)	18767 (23.1%)	<0.0001
Transplant	1318 (1.2%)	643 (2.0%)	675 (0.8%)	<0.0001
IBD	1616 (1.4%)	927 (2.9%)	689 (0.9%)	<0.0001
IBS	1193 (1.1%)	367 (1.2%)	826 (1.0%)	0.0302
VA Frailty Index*	0.11 (0.06-0.18)	0.16 (0.07-0.23)	0.10 (0.06-0.16)	<0.0001

*Median (IQR), IQR = interquartile range

**VISN= Veterans Integrated Services Network. Locations: VISN 1 (Maine, Vermont, New Hampshire, Massachusetts, Connecticut, Rhode Island), VISN 2 (New York, New Jersey), VISN 4 (Pennsylvania, Delaware, New Jersey, Ohio), VISN 5 (Maryland, West Virginia, Virginia, Kentucky, Washington D.C.) , VISN 6 (North Carolina, Virginia) , VISN 7 (South Carolina, Georgia, Alabama), VISN 8 (Florida), VISN 9 (Kentucky, Tennessee), VISN 10 (Michigan, Indiana, Ohio, Kentucky, VISN 12 (Wisconsin, Illinois, Indiana, Michigan), VISN 15 (Kansas, Missouri, Illinois, Indiana, Kentucky), VISN 16 (Arkansas, Mississippi, Louisiana), VISN 17 (Texas), VISN 19 (Montana, Wyoming, Colorado, Utah, Oklahoma, Nevada), VISN 20 (Washington, Oregon, Idaho, Alaska, Montana, VISN 21 (California, Nevada, Hawaii, Philippines Islands, Guam, American Samoa), VISN 22 (Arizona, New Mexico, California, Nevada), VISN 23 (North Dakota, Minnesota, South Dakota, Nebraska, Iowa, Wisconsin, Illinois)

Results of specific aim 1: Describe the short-term health outcomes of CDI in a national retrospective veteran cohort

Hypothesis 1.1: CDI patients will experience earlier mortality over 1-, 3-, and 12-month follow-up periods compared to non-CDI controls

After assessment of baseline characteristics, the CDI and control cohorts were propensity score matched based on factors that may have influenced CDI risk, including fiscal year, encounter setting, patient demographics (age, sex, race, ethnicity, VISN, priority group), comorbidities (Charlson, Selim, and other) in the year prior to the index encounter, healthcare exposures in the prior year (inpatient/outpatient visits, dialysis, LTCF residence), medication exposures (antibiotics, GAS medications, opioids, motility agents, and cancer chemotherapy) in the prior 90 days, and baseline VHA frailty index. Following matching, the distribution of these characteristics between cohorts was well-balanced (Table 5.2), though some remained statistically significantly different between groups due to the large sample size despite small absolute differences between cohorts.

Table 5.2. Patient baseline characteristics of matched cohorts for mortality.

	Total N (%) (n=29,872)	CDI Cohort N (%) (n=14,936)	Non-CDI Cohort N (%) (n=14,936)	P-value
Fiscal year				0.3843
2003	669 (2.2%)	352 (2.4%)	317 (2.1%)	
2004	1070 (3.6%)	547 (3.7%)	523 (3.5%)	
2005	1213 (4.1%)	636 (4.3%)	577 (3.9%)	
2006	1257 (4.2%)	647 (4.3%)	610 (4.1%)	
2007	1265 (4.2%)	627 (4.2%)	638 (4.3%)	
2008	1292 (4.3%)	655 (4.4%)	637 (4.3%)	
2009	1314 (4.4%)	652 (4.4%)	662 (4.4%)	
2010	1649 (5.5%)	784 (5.3%)	865 (5.8%)	
2011	2551 (8.5%)	1255 (8.4%)	1296 (8.7%)	
2012	3054 (10.2%)	1516 (10.2%)	1538 (10.3%)	
2013	3741 (12.5%)	1874 (12.5%)	1867 (12.5%)	
2014	3666 (12.3%)	1842 (12.3%)	1824 (12.2%)	
2015	3396 (11.4%)	1705 (11.4%)	1691 (11.3%)	
2016	141 (0.5%)	61 (0.4%)	80 (0.5%)	
2017	371 (1.2%)	173 (1.2%)	198 (1.3%)	
2018	3223 (10.8%)	1610 (10.8%)	1613 (10.8%)	
Age*	65 (58 - 75)	65 (58 - 75)	65 (58 - 74)	0.4093
Sex				0.5786
Female	1505 (5.0%)	742 (5.0%)	763 (5.1%)	
Male	28367 (94.9%)	14194 (95.0%)	14173 (94.9%)	
Race				<0.0001
White	22287 (74.6%)	11391 (76.3%)	10896 (72.9%)	
Black	5598 (18.7%)	2391 (16.0%)	3207 (21.3%)	
Other	472 (1.6%)	254 (1.7%)	218 (1.5%)	
Missing	1515 (5.1%)	900 (6.0%)	615 (4.1%)	
Ethnicity				<0.0001
Hispanic	1173 (3.9%)	689 (4.6%)	484 (3.2%)	
Not Hispanic	28383 (95.0%)	13978 (93.6%)	14405 (96.4%)	
Missing	316 (1.1%)	269 (1.8%)	47 (0.3%)	
Setting				0.2759
Inpatient	26446 (88.5%)	13193 (88.3%)	13253 (88.7%)	
Outpatient	3426 (11.5%)	1743 (11.7%)	1683 (11.3%)	

Table 5.2, *cont.*

VHA priority group				0.0086
Group 1	6674 (22.3%)	3341 (22.4%)	3333 (22.3%)	
Group 2	1770 (5.9%)	894 (5.9%)	876 (5.9%)	
Group 3	2971 (9.9%)	1490 (9.9%)	1481 (9.9%)	
Group 4	1002 (3.4%)	530 (3.5%)	472 (3.2%)	
Group 5	13866 (46.4%)	6806 (45.6%)	7060 (47.3%)	
Group 6	727 (2.4%)	402 (2.7%)	325 (2.2%)	
Group 7	1291 (4.3%)	665 (4.5%)	626 (4.2%)	
Group 8	1571 (5.3%)	808 (5.4%)	763 (5.1%)	
Geographic region (VISN)**				<0.0001
VISN 1	1822 (6.1%)	1197 (8.0%)	625 (4.2%)	
VISN 2	1787 (5.9%)	936 (6.3%)	851 (5.7%)	
VISN 4	1090 (3.7%)	518 (3.5%)	572 (3.8%)	
VISN 5	1401 (4.7%)	701 (4.7%)	700 (4.7%)	
VISN 6	1401 (4.7%)	620 (4.2%)	781 (5.2%)	
VISN 7	1506 (5.0%)	733 (4.9%)	773 (5.2%)	
VISN 8	2629 (8.8%)	1228 (8.2%)	1401 (9.2%)	
VISN 9	1509 (5.1%)	671 (4.5%)	838 (5.6%)	
VISN 10	2097 (7.0%)	821 (5.5%)	1276 (8.5%)	
VISN 12	1805 (6.0%)	881 (5.9%)	924 (6.2%)	
VISN 15	1914 (6.4%)	1156 (7.7%)	758 (5.1%)	
VISN 16	1773 (5.9%)	745 (4.9%)	1028 (6.9%)	
VISN 17	1321 (4.4%)	613 (4.1%)	708 (4.7%)	
VISN 19	1281 (4.3%)	736 (4.9%)	545 (3.6%)	
VISN 20	1018 (3.4%)	459 (3.1%)	559 (3.7%)	
VISN 21	1387 (4.6%)	726 (4.9%)	661 (4.4%)	
VISN 22	2637 (8.8%)	1499 (10.0%)	1138 (7.6%)	
VISN 23	1494 (5.0%)	696 (4.7%)	798 (5.3%)	
Exposures in prior year				
*Inpatient visits**	0 (0-1)	1 (1)	0 (1)	<0.0001
*Outpatient visits**	25 (13 - 45)	24 (11- 44)	26 (14 - 46)	<0.0001
Chronic Dialysis	960 (3.2%)	466 (3.1%)	494 (3.3%)	0.3583
Long-term care facility	1723 (5.8%)	843 (5.6%)	880 (5.9)	0.3585

Table 5.2, *cont.*

Medications in prior 90 days				
Antibiotics	12402(41.5%)	6067(40.6%)	6335(42.4%)	0.0016
Gastric acid suppressants	13658(45.7%)	6730(45.1%)	6928(46.4%)	0.0215
Laxatives	3574 (11.9%)	1746(11.7%)	1828(12.2%)	0.1438
Anti-diarrheals	1184 (3.9%)	577 (3.9%)	607 (4.1%)	0.3736
Opioids	10825(36.2%)	5369(35.9%)	5456(36.5%)	0.2950
Cancer chemotherapy	1418 (4.8%)	686 (4.6%)	732 (4.9%)	0.2107
Charlson comorbidities in prior year				
Myocardial infarction	1802 (6.0%)	894 (5.9%)	908 (6.1%)	0.7337
Congestive heart failure	5210 (17.4%)	2599(17.4%)	2611(17.5%)	0.8548
Peripheral vascular disease	4877 (16.3%)	2404(16.1%)	2473(16.6%)	0.2801
Cerebrovascular disease	4161 (13.9%)	2064(13.8%)	2097(14.0%)	0.5813
Dementia	1058 (3.5%)	514 (3.4%)	544 (3.6%)	0.3477
Chronic pulmonary disease	9015 (30.2%)	4448(29.8%)	4567(30.6%)	0.1336
Rheumatic disease	727 (2.4%)	362 (2.4%)	365 (2.4%)	0.9103
Peptic ulcer disease	763 (2.6%)	382 (2.6%)	381 (2.6%)	0.9707
Mild liver disease	2967 (9.9%)	1522(10.2%)	1445 (9.7%)	0.1363
Diabetes w/o complications	10664(35.7%)	5305(35.5%)	5359(35.9%)	0.5143
Diabetes w/ complications	4657 (15.6%)	2317(15.5%)	2340(15.7%)	0.7137
Hemiplegia or paraplegia	1364 (4.6%)	652 (4.4%)	712 (4.8%)	0.0963
Renal disease	5459 (18.3%)	2660(17.8%)	2799(18.7%)	0.0374
Cancer	6345 (21.2%)	3105(20.8%)	3240(21.7%)	0.0562
Cancer metastasis	1046 (3.5%)	508 (3.4%)	538 (3.6%)	0.3450
Moderate/severe liver Disease	545 (1.8%)	281 (1.9%)	264 (1.8%)	0.4623
HIV/AIDS	412 (1.4%)	197 (1.3%)	215 (1.4%)	0.3719
Charlson comorbidity score*	2 (1-3)	2 (1-3)	2 (1-3)	0.0175

Table 5.2, *cont.*

Selim comorbidities in prior year				
Schizophrenia	1098 (3.7%)	551 (3.7%)	547 (3.7%)	0.9021
Depression	7450 (24.9%)	3717 (24.9%)	3733 (24.9%)	0.8306
Bipolar disorder	3340 (11.2%)	1650 (11.0%)	1690 (11.3%)	0.4627
Anxiety disorder	1701 (5.7%)	835 (5.6%)	866 (5.8%)	0.4389
Post-traumatic stress disorder	4366 (14.6%)	2149 (14.4%)	2217 (14.8%)	0.2654
Alcohol abuse	892 (2.9%)	444 (2.9%)	448 (2.9%)	0.8918
Other comorbidities in prior year				
Hypertension	20321 (68.0%)	10137 (67.9%)	10184 (68.2%)	0.5598
Dyslipidemia	1919 (6.4%)	956 (6.4%)	963 (6.5%)	0.8688
Obesity	5590 (18.7%)	2789 (18.7%)	2801 (18.8%)	0.8587
GERD	7519 (25.2%)	3694 (24.7%)	3825 (25.6%)	0.0807
Transplant	453 (1.5%)	216 (1.5%)	237 (1.6%)	0.3200
IBD	672 (2.3%)	336 (2.3%)	336 (2.3%)	1.0000
IBS	315 (1.1%)	156 (1.0%)	159 (1.1%)	0.8651
VA Frailty Index*	0.129 (0.65-0.19)	0.129 (0.65-0.19)	0.129 (0.65-0.19)	0.0685

Our primary outcome, all-cause mortality, was assessed at 1-, 3-, and 12-month intervals. A total of 29,872 (14,936 CDI and 14,936 non-CDI controls) patients were available for all-cause mortality analyses. Mortality was common among CDI patients; at 12 months, more than a quarter (27.7%) of CDI patients had died compared to only 7.6% among controls. Mortality risk was significantly higher in the CDI cohort for all three short-term follow-up periods (adjusted OR, 99% CI): 1 month (3.75, 3.23-4.34), 3 months (3.07, 2.74-3.43), and 12 months (2.70, 2.47-2.96) (Table 5.3). The absolute mortality risk difference between cohorts increased over time, but after adjustment for covariates, the relative risk of mortality between cohorts decreased over time. Other significant predictors

of mortality at 12 months included: metastatic cancer (OR 4.43, 99% CI 3.81-5.14), moderate/severe liver disease (OR 2.50, 99% CI 1.99-3.13), concomitant pneumonia (OR 1.78, 99% CI 1.64-1.94), shock (OR 1.36, 99% CI 1.14-1.61), and acute renal failure (OR 1.35, 99% CI 1.24-1.48).

Table 5.3. Prevalence of mortality at follow-up

	CDI Cohort (n=9,475)	Non-CDI Cohort (n=9,475)	P-value	OR (99% CI)	Adjusted OR (99% CI)[a]
1 month	1942 (13.0%)	308 (2.1%)	<0.0001	7.09 (6.28, 8.02)	3.75 (3.23-4.34)[b]
3 months	2686 (17.9%)	555 (3.7%)	<0.0001	5.68 (5.17, 6.24)	3.07 (2.74-3.43)[b]
12 months	4136 (27.7%)	1131 (7.6%)	<0.0001	4.67 (5.17, 6.24)	2.70 (2.47-2.96)[b]

[a]1 month and 3 month covariates included: bacteremia, pneumonia, skin infection, endocarditis, UTI, device infection, ART, shock, sepsis, perforated intestine, ileus, megacolon, acute renal failure, concomitant antibiotics, concomitant gastric acid suppressants, WBC, CRP, albumin, SCr, concomitant opioids, concomitant anti-diarrheals, concomitant laxatives, ICU stay, hospital length of stay. 12 month covariates included 1 and 3 month covariates plus the following assessed during 12 months of follow-up: hypertension, dyslipidemia, irritable bowel disease, irritable bowel syndrome, obesity, GERD, transplant, schizophrenia, depression, bipolar, anxiety, PTSD, alcohol abuse, CHF, peripheral vascular disease, COPD, rheumatic disease, any liver disease, diabetes w/ and w/o complications, hemi/paraplegia, HIV/AIDS, any antibiotics (including high risk), in/outpatient visits, dialysis, LTCF stay.
[b]Adjusted p<0.0001

Survival analysis was performed and is presented using Kaplan Meier curves in Figures 5.1, 5.2, and 5.3, excluding patients who died during the encounter (0 days to death). In univariate analysis using the log-rank test, mortality was significantly higher among CDI patients (p<0.0001). Using a Cox proportional hazards model that included covariates, CDI significantly predicted mortality at 1 month, 3 months, and 12 months (p<0.0001 for all).

Figure 5.1. Kaplan Meier survival curve for mortality at 1 month

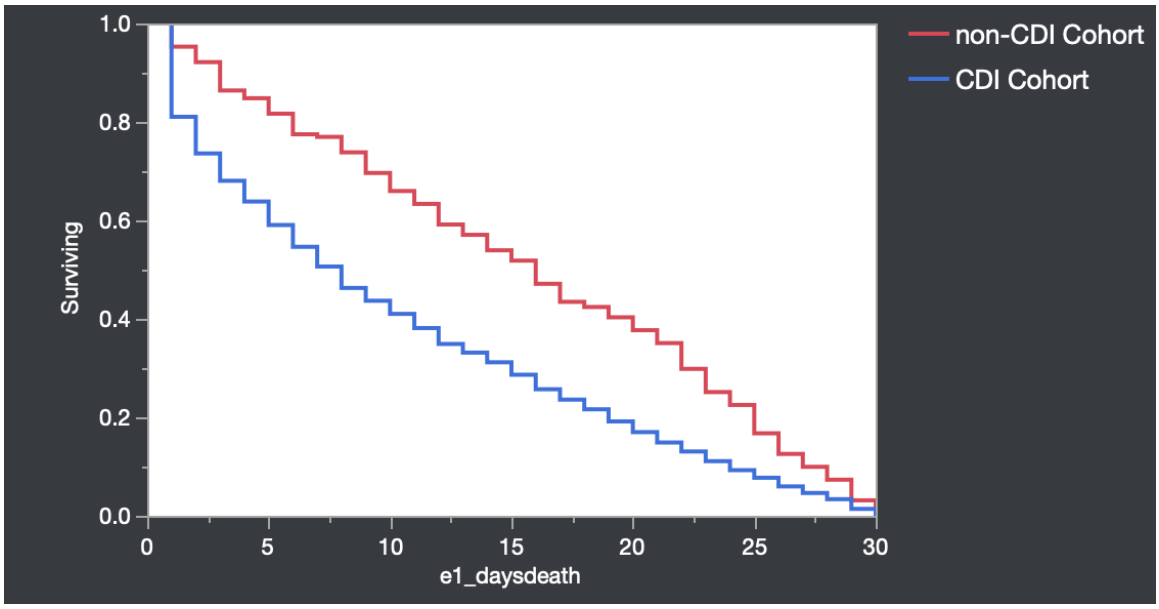


Figure 5.2. Kaplan Meier survival curve for mortality at 3 months

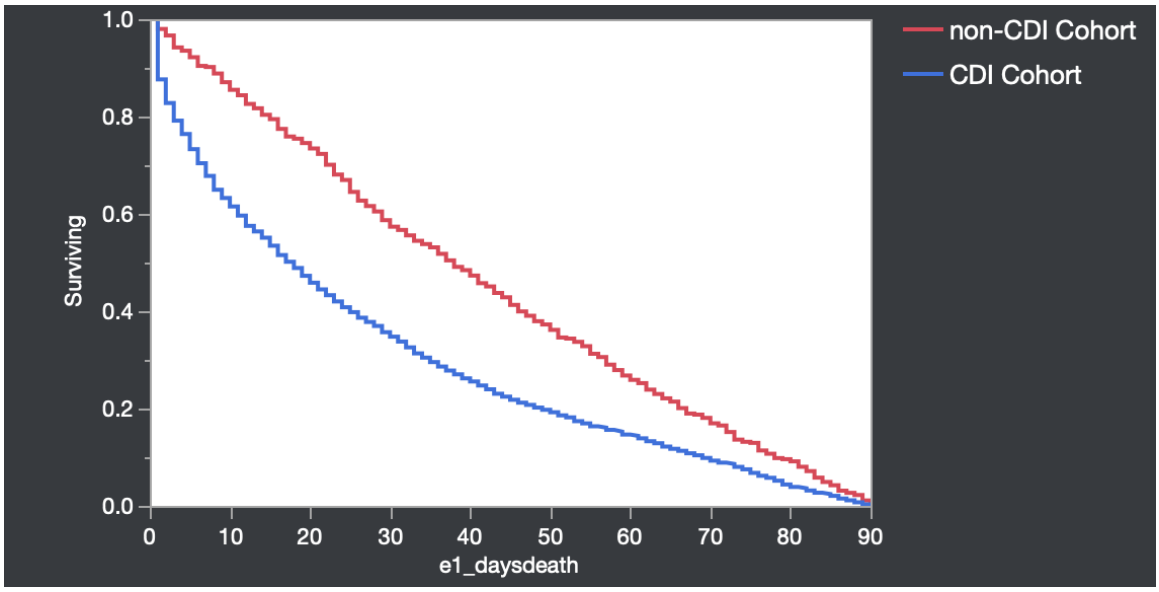
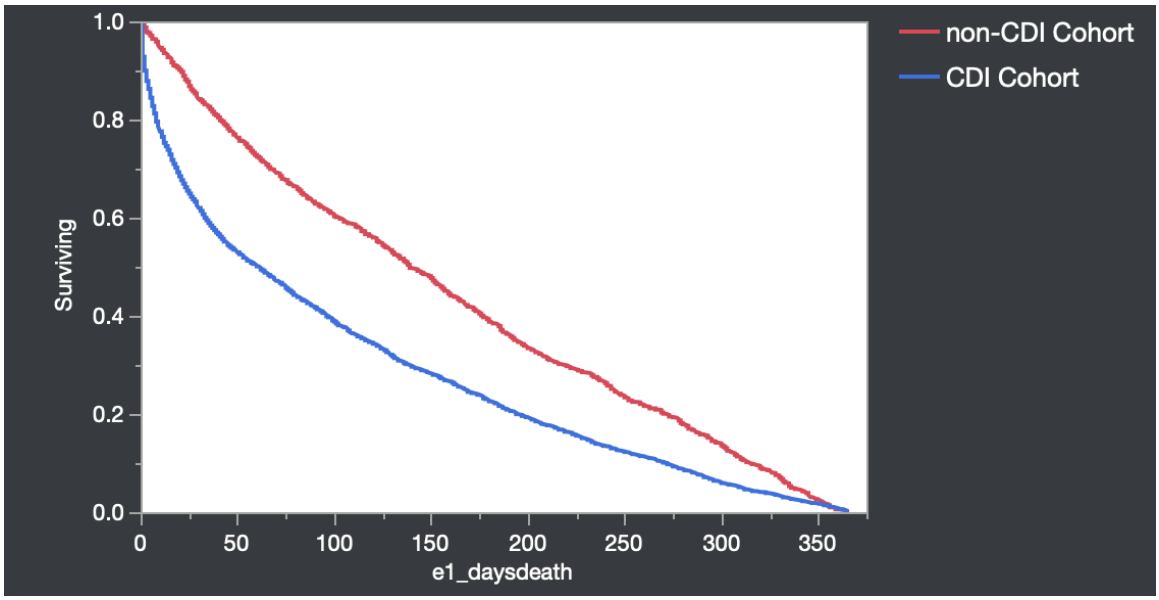


Figure 5.3. Kaplan Meier survival curve for mortality at 12 months



Hypothesis 1.2: CDI patients will experience more aging-related conditions over 1-, 3-, and 12-month follow-up periods compared to non-CDI controls.

For analyses of aging-related condition outcomes during follow-up, we excluded a total of 33,883 (30.0%) patients from the unmatched cohorts (13,681 CDI and 20,202 controls) who had aging-related conditions at baseline. The cohorts were then propensity score matched similarly as described for mortality analyses. Following matching, there were a total of 9,475 patients in each group (18,950 patients total) for analyses. CDI and control patients were well-matched in regard to baseline demographics, prior healthcare exposures, prior medication exposures, and prior comorbidities (Table 5.4).

Table 5.4. Patient baseline characteristics of matched cohorts for aging-related conditions.

	Total N (%) (n=18,950)	CDI Cohort N (%) (n=9,475)	Non-CDI Cohort N (%) (n=9,475)	P-value
Fiscal year				0.2311
2003	441 (2.3%)	229 (2.4%)	212 (2.2%)	
2004	672 (3.5%)	348 (3.7%)	324 (3.4%)	
2005	764 (4.0%)	401 (4.2%)	363 (3.8%)	
2006	771 (4.1%)	399 (4.2%)	372 (3.9%)	
2007	781 (4.1%)	402 (4.2%)	379 (4.0%)	
2008	823 (4.3%)	423 (4.5%)	400 (4.2%)	
2009	830 (4.4%)	387 (4.1%)	443 (4.7%)	
2010	967 (5.1%)	469 (4.9%)	498 (5.3%)	
2011	1605 (8.5%)	769 (8.1%)	836 (8.8%)	
2012	1900 (10.3%)	958 (10.1%)	942 (9.9%)	
2013	2317 (12.2%)	1164 (12.3%)	1153 (12.2%)	
2014	2283 (12.0%)	1155 (12.2%)	1128 (11.9%)	
2015	2193 (11.6%)	1114 11.8(%)	1079 (11.4%)	
2016	88 (0.5%)	39 (0.4%)	49 (0.5%)	
2017	260 (1.4%)	119 (1.3%)	141 (1.5%)	
2018	2255 (11.9%)	1099 (11.6%)	1156 (12.2%)	
Age*	63 (55-72)	63 (55-72)	63 (55-71)	0.0896
Sex				0.9272
Female	1149 (6.1%)	573 (6.0%)	576 (6.1%)	
Male	17801 (93.9%)	8902 (93.9%)	8899 (93.9%)	
Race				<0.0001
White	14056 74.2(%)	7213 (76.1%)	6843 (72.2%)	
Black	3611 (19.1%)	1516 (16.0%)	2095 (22.1%)	
Other	348 (1.8%)	176 (1.9%)	172 (1.8%)	
Missing	935 (4.9%)	570 (6.0%)	365 (3.9%)	
Ethnicity				<0.0001
Hispanic	850 (4.2%)	473 (4.9%)	332 (3.5%)	
Not Hispanic	17944 (94.7%)	8823 (93.1%)	9121 (96.3%)	
Missing	201 (1.1%)	179 (1.9%)	22 (0.2%)	

Table 5.4, *cont.*

Setting				0.1676
Inpatient	16476 (86.9%)	8206 (86.6%)	8270 (87.3%)	
Outpatient	2474 (13.1%)	1269 (13.4%)	1205 (12.7%)	
VHA priority group				0.0008
Group 1	4305 (22.7%)	2135 (22.5%)	2170 (22.9%)	
Group 2	1183 (6.2%)	592 (6.2%)	591 (6.2%)	
Group 3	1945 (10.3%)	1004 (10.6%)	941 (9.9%)	
Group 4	636 (3.4%)	337 (3.6%)	299 (3.2%)	
Group 5	8741 (46.1%)	4256 (44.9%)	4485 (47.3%)	
Group 6	465 (2.5%)	263 (2.8%)	202 (2.1%)	
Group 7	726 (3.8%)	389 (4.1%)	337 (3.6%)	
Group 8	949 (5.0%)	499 (5.3%)	450 (4.7%)	
Geographic region (VISN)**				<0.0001
VISN 1				
VISN 2	1122 (5.9%)	742 (7.6%)	398 (4.2%)	
VISN 4	1035 (5.5%)	566 (5.9%)	469 (4.9%)	
VISN 5	698 (3.7%)	317 (3.3%)	381 (4.0%)	
VISN 6	861 (4.5%)	422 (4.5%)	439 (4.6%)	
VISN 7	911 (4.8%)	415 (4.4%)	496 (5.2%)	
VISN 8	1006 (5.3%)	490 (5.2%)	516 (5.4%)	
VISN 9	1631 (8.6%)	771 (8.1%)	860 (9.1%)	
VISN 10	930 (4.9%)	430 (4.5%)	500 (5.3%)	
VISN 12	1293 (6.8%)	500 (5.3%)	793 (8.4%)	
VISN 15	1146 (6.0%)	583 (6.2%)	563 (5.9%)	
VISN 16	1196 (6.3%)	731 (7.7%)	465 (4.9%)	
VISN 17	1122 (5.9%)	473 (4.9%)	649 (6.9%)	
VISN 19	894 (4.7%)	398 (4.2%)	496 (5.2%)	
VISN 20	854 (4.5%)	498 (5.3%)	356 (3.8%)	
VISN 21	681 (3.6%)	289 (3.1%)	392 (4.1%)	
VISN 22	879 (4.6%)	456 (4.8%)	423 (4.5%)	
VISN 23	1713 (9.0%)	955 (10.1%)	758 (8.0%)	
	978 (5.2%)	457 (4.8%)	521 (5.5%)	
Exposures in prior year				
*Inpatient visits**	0 (0-1)	0 (0-1)	0 (0-1)	<0.0001
*Outpatient visits**	21 (10-39)	19 (8-38)	23 (11-40)	<0.0001
Chronic Dialysis	584 (3.1%)	277 (2.9%)	307 (3.2%)	0.2072
Long-term care facility	941 (4.9%)	454 (4.8%)	487 (5.1%)	0.2073

Table 5.4, *cont.*

Medications in prior 90 days				
Antibiotics	7358 (38.8%)	3615(38.2%)	3743(39.5%)	0.0564
Gastric acid suppressants	7950 (41.9%)	3920(41.4%)	403(42.5%)	0.1054
Laxatives	1940 (10.2%)	941 (9.9%)	999 (10.5%)	0.1645
Anti-diarrheals	670 (3.5%)	327 (3.5%)	343 (3.6%)	0.5291
Opioids	6251 (32.9%)	3106(32.8%)	3145(33.2%)	0.5468
Cancer chemotherapy	177 (0.9%)	94 (0.9%)	83 (0.9%)	0.4060
Charlson comorbidities in prior year				
Myocardial infarction	-	-	-	-
Congestive heart failure	2822 (14.9%)	1392(14.7%)	1430(15.1%)	0.4381
Peripheral vascular disease	2520 (13.3%)	1224(12.9%)	1296(13.7%)	0.1235
Cerebrovascular disease	-	-	-	-
Dementia	-	-	-	-
Chronic pulmonary disease	5079 (26.8%)	2512(26.5%)	2567(27.1%)	0.3670
Rheumatic disease	428 (2.3%)	212 (2.2%)	216 (2.3%)	0.8449
Peptic ulcer disease	412 (2.2%)	208 (2.2%)	204 (2.2%)	0.8421
Mild liver disease	2031 (10.7%)	1013(10.7%)	1018(10.7%)	0.9065
Diabetes w/o complications	6281(33.1%)	3125(32.9%)	3156(33.3%)	0.6324
Diabetes w/ complications	2753 (14.5%)	1354(14.3%)	1399(14.8%)	0.3536
Hemiplegia or paraplegia	852 (4.5%)	406 (4.3%)	446 (4.7%)	0.1608
Renal disease	3020 (15.9%)	1461(15.4%)	1559(16.5%)	0.0518
Cancer	-	-	-	-
Cancer metastasis	-	-	-	-
Moderate/severe liver	367 (1.9%)	179 (1.9%)	188 (1.9%)	0.6352
Disease	314 (1.7%)	164 (1.7%)	150 (1.6%)	0.4256
HIV/AIDS				
Charlson comorbidity score*	1 (0-2)	1 (0-2)	1 (0-2)	0.0076

Table 5.4, *cont.*

Selim comorbidities in prior year				
Schizophrenia	714 (3.8%)	348 (3.7%)	366 (3.9%)	0.4923
Depression	4591 (24.2%)	2277 (24.0%)	2314 (24.4%)	0.5304
Bipolar disorder	2249 (11.9%)	1096 (11.6%)	1153 (12.2%)	0.2004
Anxiety disorder	1124 (5.9%)	540 (5.7%)	584 (6.2%)	0.1760
Post-traumatic stress disorder	2862 (15.1%)	1417 (14.9%)	1445 (15.3%)	0.5700
Alcohol abuse	694 (3.7%)	330 (3.5%)	364 3.8(%)	0.1884
Other comorbidities in prior year				
Hypertension	11825 (62.4%)	5856 (61.8%)	5969 (62.9%)	0.0901
Dyslipidemia	1246 (6.6%)	613 (6.5%)	633 (6.7%)	0.5577
Obesity	3587 (18.9%)	1798 (18.9%)	1789 (18.9%)	0.8675
GERD	4451 (23.5%)	2213 (23.4%)	2238 (23.6%)	0.6684
Transplant	270 (1.4%)	129 (1.4%)	141 (1.5%)	0.4619
IBD	494 (2.6%)	244 (2.6%)	250 (2.6%)	0.7844
IBS	238 (1.3%)	124 (1.3%)	114 (1.2%)	0.5141
VA Frailty Index*	0.096 (0.065-0.161)	0.097 (0.032-0.161)	0.097 (0.645-0.161)	0.0058

At 1 month, 3 months, and 12 months post-index encounter, there were no significant differences in the development of aging-related conditions in CDI patients compared to controls in bivariable analyses using a p-value cutoff of <0.0001 (Table 5.5). Aging-related conditions were numerically higher in the CDI cohort at 1 month and 3 months, but then numerically higher among controls at 12 months. At 12-months, only cancer and neurodegenerative disease were higher in proportions of CDI patients compared to non-CDI controls; however, these differences were not statistically significant (Table 5.5). In the regression model, CDI was an independent predictor of a cancer diagnosis at 1 month follow up (OR 1.27, 99% CI 1.03-1.57), though it was not a

predictor at later follow up of 3 and 12 months, which will be discussed further in the next chapter (Table 5.5). Other significant predictors of aging-related conditions at 12-months included: hypertension at 1 year (OR 1.86, 99% CI 1.64-2.11), peripheral vascular disease at 1 year (OR 1.48, 99% CI 1.31-1.67), and ICU admission during the index encounter (OR 1.31, 99% CI 1.16-1.49). Among CDI patients only, there was no significant association between the number of CDI episodes and the development of aging-related conditions at 12 months (p=0.2078).

Table 5.5. Prevalence of aging-related conditions at follow-up in matched cohorts

	CDI Cohort	Non-CDI Cohort	P-value	OR (99% CI)	Adjusted OR (99% CI)[a]
1 month	**n=8432**	**n=9363**			
Any aging condition	576 (6.8%)	521 (5.6%)	0.0005	1.24 (1.10-1.41)	0.82 (0.70-0.96)[b]
Cardiovascular disease	231 (2.7%)	222 (2.4%)	0.1194	1.16 (0.96-1.39)	0.84 (0.67-1.07)
Cancer	297 (3.5%)	251 (2.7%)	0.0021	1.26 (1.09-1.47)	1.27 (1.03-1.57)[b]
Neurodegenerative disease	83 (0.9%)	64 (0.7%)	0.0269	1.44 (1.04-2.00)	0.83 (0.56-1.23)
3 months	**n=8059**	**n=9275**			
Any aging condition	801 (9.9%)	852 (9.2%)	0.0924	1.09 (0.99-1.21)	0.79 (0.69-0.90)[b]
Cardiovascular disease	321 (4.0%)	404 (4.4%)	0.2210	0.91 (0.78-1.06)	0.68 (0.56-0.82)[c]
Cancer	398 (4.9%)	388 (4.2%)	0.0173	1.19 (1.03-1.37)	0.81 (0.68-0.97)[b]
Neurodegenerative disease	140 (1.7%)	113 (1.2%)	0.0046	1.43 (1.12-1.84)	1.31 (0.97-1.78)
12 months	**n=7293**	**n=9011**			
Any aging condition	1135 (15.6%)	1470 (16.3%)	0.1931	0.95 (0.87-1.03)	0.99 (0.89-1.11)

Table 5.5, *cont.*

Cardiovascular disease	565 (7.7%)	821 (9.1%)	0.0018	0.84 (0.75-0.94)	0.96 (0.83-1.12)
Cancer	458 (6.3%)	530 (5.9%)	0.2897	1.07 (0.94-1.22)	1.01 (0.86-1.20)
Neurodegenerative disease	240 (3.3%)	261 (2.9%)	0.1476	1.14 (0.95-1.36)	1.21 (0.96-1.52)

[a]1 month and 3 month covariates included: bacteremia, pneumonia, skin infection, endocarditis, UTI, device infection, ART, shock, sepsis, perforated intestine, ileus, megacolon, acute renal failure, concomitant antibiotics, concomitant gastric acid suppressants, WBC, CRP, albumin, SCr, concomitant opioids, concomitant anti-diarrheals, concomitant laxatives, ICU stay, hospital length of stay. 12 month covariates included 1 and 3 month covariates plus the following assessed during 12 months of follow-up: hypertension, dyslipidemia, irritable bowel disease, irritable bowel syndrome, obesity, GERD, transplant, schizophrenia, depression, bipolar, anxiety, PTSD, alcohol abuse, CHF, peripheral vascular disease, COPD, rheumatic disease, any liver disease, diabetes w/ and w/o complications, hemi/paraplegia, HIV/AIDS, any antibiotics (including high risk), in/outpatient visits, dialysis, LTCF stay.
[b]Adjusted $p>0.0001$
[c]Adjusted $p<0.0001$

Hypothesis 1.3: CDI patients will experience more frailty-associated diagnoses over 1-, 3-, and twelve-month follow-up periods compared to non-CDI controls

For analyses of frailty-associated condition outcomes during follow-up, we excluded a total of 32,771 (29.05%) patients from the unmatched cohorts (14,335 CDI and 18,436 controls) who had frailty-associated conditions at baseline. Following propensity score matching, there were a total of 9,499 patients in each group (18,998 patients total) for analyses. CDI and control patients were well-matched in regard to baseline demographics, prior healthcare exposures, prior medication exposures, and prior comorbidities (Table 5.6).

Table 5.6. Patient baseline characteristics of matched cohorts for frailty-associated conditions

	Total N (%) (n=18,998)	CDI Cohort N (%) (n=9,499)	Non-CDI Cohort N (%) (n=9,499)	P-value
Fiscal year				0.0121
2003	461 (2.4%)	245 (2.6%)	216 (2.3%)	
2004	698 (3.7%)	361 (3.8%)	337 (3.5%)	
2005	838 (4.4%)	447 (4.7%)	391 (4.1%)	
2006	806 (4.2%)	417 (4.4%)	389 (4.1%)	
2007	789 (4.2%)	396 (4.2%)	393 (4.1%)	
2008	837 (4.4%)	413 (4.3%)	424 (4.5%)	
2009	787 (4.1%)	393 (4.1%)	394 (4.2%)	
2010	1007 (5.3%)	493 (5.2%)	514 (5.4%)	
2011	1503 (7.9%)	714 (7.5%)	789 (8.3%)	
2012	1894 (10.0%)	947 (10.0%)	947 (10.0%)	
2013	2328 (12.3%)	1208 (12.7%)	1120 (11.8%)	
2014	2314 (12.2%)	1161 (12.2%)	1153 (12.1%)	
2015	2136 (11.2%)	1047 (11.0%)	1089 (11.5%)	
2016	95 (0.5%)	35 (0.4%)	60 (0.6%)	
2017	279 (1.5%)	117 (1.2%)	162 (1.7%)	
2018	2226 (11.7%)	1105 (11.6%)	1121 (11.8%)	
Age*	65 (57-73)	65 (57-74)	64 (56-72)	0.0015
Sex				0.3047
Female	1097 (5.8%)	532 (5.6%)	565 (5.9%)	
Male	17901 (94.2%)	8967 (94.4%)	8934 (94.1%)	
Race				<0.0001
White	14299 (75.3%)	7366 (77.5%)	6933 (73.0%)	
Black	3422 (18.0%)	1371 (14.4%)	2051 (21.6%)	
Other	304 (1.6%)	162 (1.7%)	142 (1.5%)	
Missing	973 (5.1%)	600 (6.3%)	373 (3.9%)	
Ethnicity				<0.0001
Hispanic	759 (4.0%)	439 (4.6%)	320 (3.4%)	
Not Hispanic	18009 (94.8%)	8854 (93.2%)	9155 (96.4%)	
Missing	230 (1.2%)	206 (2.2%)	24 (0.3%)	

Table 5.6, *cont.*

Setting				0.6385
Inpatient	16468 (86.7%)	8223 (86.6%)	8245 (86.8%)	
Outpatient	2530 (13.3%)	1276 (13.4%)	1254 (13.2%)	
VHA priority group				0.0749
Group 1	4257 (22.4%)	2090 (22.0%)	2167 (22.8%)	
Group 2	1105 (5.8%)	544 (5.7%)	561 (5.9%)	
Group 3	1972 (10.4%)	1002 (10.5%)	970 (10.2%)	
Group 4	615 (3.2%)	338 (3.6%)	277 (2.9%)	
Group 5	8688 (45.7%)	4300 (45.3%)	4388 (46.2%)	
Group 6	510 (2.7%)	270 (2.8%)	240 (2.5%)	
Group 7	823 (4.3%)	421 (4.4%)	402 (4.2%)	
Group 8	1028 (5.4%)	534 (5.6%)	494 (5.2%)	
Geographic region (VISN)**				<0.0001
VISN 1	1152 (6.1%)	767 (8.1%)	385 (4.1%)	
VISN 2	1112 (5.9%)	566 (6.0%)	546 (5.7%)	
VISN 4	714 (3.8%)	343 (3.6%)	371 (3.9%)	
VISN 5	847 (4.5%)	428 (4.55)	419 (4.4%)	
VISN 6	915 (4.8%)	387 (4.1%)	528 (5.6%)	
VISN 7	997 (5.2%)	488 (5.1%)	509 (5.4%)	
VISN 8	1553 (8.2%)	769 (8.1%)	784 (8.3%)	
VISN 9	962 (5.1%)	424 (4.5%)	538 (5.7%)	
VISN 10	1299 (6.8%)	509 (5.4%)	790 (8.3%)	
VISN 12	1150 (6.1%)	583 (6.1%)	567 (6.0%)	
VISN 15	1204 (6.3%)	731 (7.7%)	473 (5.0%)	
VISN 16	1159 (6.1%)	472 (5.0%)	687 (7.2%)	
VISN 17	841 (4.4%)	360 (3.8%)	481 (5.1%)	
VISN 19	880 (4.6%)	501 (5.3%)	379 (4.0%)	
VISN 20	689 (3.6%)	308 (3.25)	381 (4.0%)	
VISN 21	838 (4.4%)	446 (4.7%)	392 (4.1%)	
VISN 22	1732 (9.1%)	953 (10.0%)	779 (8.2%)	
VISN 23	954 (5.0%)	464 (4.9%)	490 (5.2%)	
Exposures in prior year				
*Inpatient visits**	0 (0-1)	0 (0-1)	0 (0-1)	<0.0001
*Outpatient visits**	20 (9-36)	18 (8-34)	21 (11-37)	<0.0001
Chronic Dialysis	253 (1.3%)	117 (1.2%)	136 (1.4%)	0.2289
Long-term care facility	727 (3.8%)	354 (3.7%)	373 (3.9%)	0.4724

Table 5.6, *cont.*

Medications in prior 90 days				
Antibiotics	7303 (38.4%)	3553 (37.4%)	3750 (39.5%)	0.0033
Gastric acid suppressants	7449 (39.2%)	3704 (39.4%)	3745 (39.4%)	0.5423
Laxatives				
Anti-diarrheals	1839 (9.7%)	894 (9.4%)	945 (9.9%)	0.2108
Opioids	656 (3.5%)	314 (3.3%)	342 (3.6%)	0.2658
Cancer chemotherapy	5999 (31.6%)	2972 (31.3%)	3027 (31.9%)	0.3906
	686 (3.6%)	331 (3.5%)	355 (3.7%)	0.3506
Charlson comorbidities in prior year				
Myocardial infarction	912 (4.8%)	435 (4.6%)	477 (5.0%)	0.1540
Congestive heart failure	2391 (12.6%)	1186 (12.5%)	1205 (12.7%)	0.6777
Peripheral vascular disease	2612 (13.7%)	1278 (13.5%)	1334 (14.0%)	0.2381
Cerebrovascular disease	2195 (11.6%)	1084 (11.4%)	1111 (11.7%)	0.5400
Dementia	502 (2.6%)	242 (2.5%)	260 (2.7%)	0.4155
Chronic pulmonary disease	5059 (26.6%)	2489 (26.2%)	2570 (27.1%)	0.1837
Rheumatic disease	362 (1.9%)	174 (1.8%)	188 (2.0%)	0.4575
Peptic ulcer disease	317 (1.7%)	153 (1.6%)	164 (1.7%)	0.5332
Mild liver disease	1482 (7.8%)	730 (7.7%)	752 (7.9%)	0.5517
Diabetes w/o complications	5863 (30.9%)	2929 (30.8%)	2934 (30.9%)	0.9374
Diabetes w/ complications	2302 (12.1%)	1136 (12.0%)	1166 (12.3%)	0.5048
Hemiplegia or paraplegia	861 (4.5%)	413 (4.3%)	448 (4.7%)	0.2221
Renal disease	2176 (11.5%)	1068 (11.2%)	1108 (11.7%)	0.3621
Cancer	3474 (18.1%)	1667 (17.5%)	1767 (18.6%)	0.0594
Cancer metastasis	480 (2.5%)	222 (2.3%)	258 (2.7%)	0.0959
Moderate/severe liver disease	201 (1.1%)	95 (1.0%)	106 (1.1%)	0.4353
HIV/AIDS	228 (1.2%)	111 (1.2%)	117 (1.2%)	0.6893
Charlson comorbidity score, median (IQR)	1 (0-3)	1 (0-3)	1 (0-3)	0.0015

Table 5.6, *cont.*

Selim comorbidities in prior year				
Schizophrenia	661 (3.5%)	313 (3.3%)	348 (3.7%)	0.1658
Depression	4166 (21.9%)	2075 (21.8%)	2091 (22.0%)	0.7791
Bipolar disorder	1979 (10.4%)	971 (10.2%)	1008 (10.6%)	0.3795
Anxiety disorder	997 (5.2%)	495 (5.2%)	502 (5.3%)	0.8198
Post-traumatic stress disorder	2708 (14.3%)	1326 (14.0%)	1382 (14.5%)	0.2452
Alcohol abuse	471 (2.5%)	227 (2.4%)	244 (2.6%)	0.4276
Other comorbidities in prior year				
Hypertension	11712 (61.6%)	5827 (61.3%)	5885 (62.0%)	0.3868
Dyslipidemia	1203 (6.3%)	593 (6.2%)	610 (6.4%)	0.6125
Obesity	3539 (18.6%)	1756 (18.5%)	1783 (18.8%)	0.6149
GERD	4284 (22.6%)	2114 (22.3%)	2170 (22.8%)	0.3309
Transplant	212 (1.1%)	104 (1.1%)	108 (1.1%)	0.7823
IBD	434 (2.3%)	204 (2.1%)	230 (2.4%)	0.2066
IBS	218 (1.1%)	107 (1.1%)	111 (1.2%)	0.7852
VA Frailty Index, median (IQR)	0.096 (0.06-0.16)	0.096 (0.03-1.6)	0.096 (0.07-0.16)	0.0012

In bivariable analyses, CDI patients were more likely to experience any frailty-related condition at 1 month (8.6% vs. 6.2%, p<0.0001), 3 months (15.1% vs. 11.2%, p<0.0001), and 12 months (26.8% vs. 23.5%, p<0.0001) (Table 5.7). These differences were driven primarily by a higher prevalence of involuntary weight loss and anemia in CDI patients at follow-up compared to controls. After adjustment for covariates at 12 months, CDI was significantly associated with the development of frailty-associated conditions (OR 1.27, 99% CI 1.15-1.41) (Table 5.7). Specifically, CDI was significantly associated with the development of coagulopathy (OR 1.84, 99% CI 1.33-2.54) and weight loss (OR 1.42, 99% CI 1.14-1.77) at 12 months. Other significant predictors of

frailty-associated conditions at 12-months included: dialysis at 1 year (OR 2.41, 99% CI 1.78-3.26), moderate/severe liver disease (OR 2.32, 99% CI 1.69-3.20), renal disease at 1 year (OR 1.75, 99% CI 1.54-1.99), cancer at 1 year (OR 1.43, 99% CI 1.28-1.59), laxative use at 1 year (OR 1.46, 99% CI 1.31-1.62), and LTFC residence at 1 year (OR 1.41, 99% CI 1.19-1.66).

Table 5.7. Prevalence of frailty-associated conditions at follow-up in matched cohorts

	CDI Cohort	Non-CDI Cohort	P-value	OR (99% CI)	Adjusted OR (99% CI)[a]
1 month	**n=8387**	**n=9350**			
Any frailty condition	718 (8.6%)	582 (6.2%)	<0.0001	1.41 (1.26-1.58)	0.82 (0.73-0.97)[b]
Coagulopathy	34 (0.4%)	34 (0.4%)	0.6535	1.12 (0.69-1.80)	1.08 (0.61-1.91)
Weight loss	96 (1.1%)	55 (0.6%)	<0.0001	1.96 (1.40-2.73)	1.43 (0.95-2.15)
Fluid & electrolyte imbalance	9 (0.1%)	2 (<0.1%)	0.0215	5.02 (1.08-23.24)	3.24 (0.56-18.9)
Anemia	522 (6.2%)	405 (4.3%)	<0.0001	1.47 (1.28-1.67)	0.76 (0.65-0.89)
Falls	44 (0.5%)	37 (0.4%)	0.2041	1.33 (0.86-2.06)	0.92 (0.55-1.54)
Fractures	70 (0.8%)	93 (1.0%)	0.2638	0.84 (0.61-1.14)	0.82 (0.56-1.19)
3 months	**n=8015**	**n=9241**			
Any frailty condition	1214 (15.1%)	1037 (11.2%)	<0.0001	1.41 (1.29-1.54)	0.89 (0.80-1.00)
Coagulopathy	70 (0.9%)	55 (0.6%)	0.0319	1.47 (1.03-2.10)	1.44 (0.93-2.23)
Weight loss	179 (2.2%)	125 (1.4%)	<0.0001	1.67 (1.32-2.10)	1.18 (0.89-1.57)
Fluid & electrolyte imbalance	15 (0.2%)	4 (<0.1%)	0.0040	4.32 (1.44-13.05)	3.99 (1.14-13.95)
Anemia	864 (10.8%)	722 (7.8%)	<0.0001	1.43 (1.29-1.58)	0.82 (0.72-0.93)
Falls	88 (1.1%)	72 (0.8%)	0.0296	1.43 (0.91-2.24)	0.92 (0.63-1.36)

Table 5.7, *cont.*

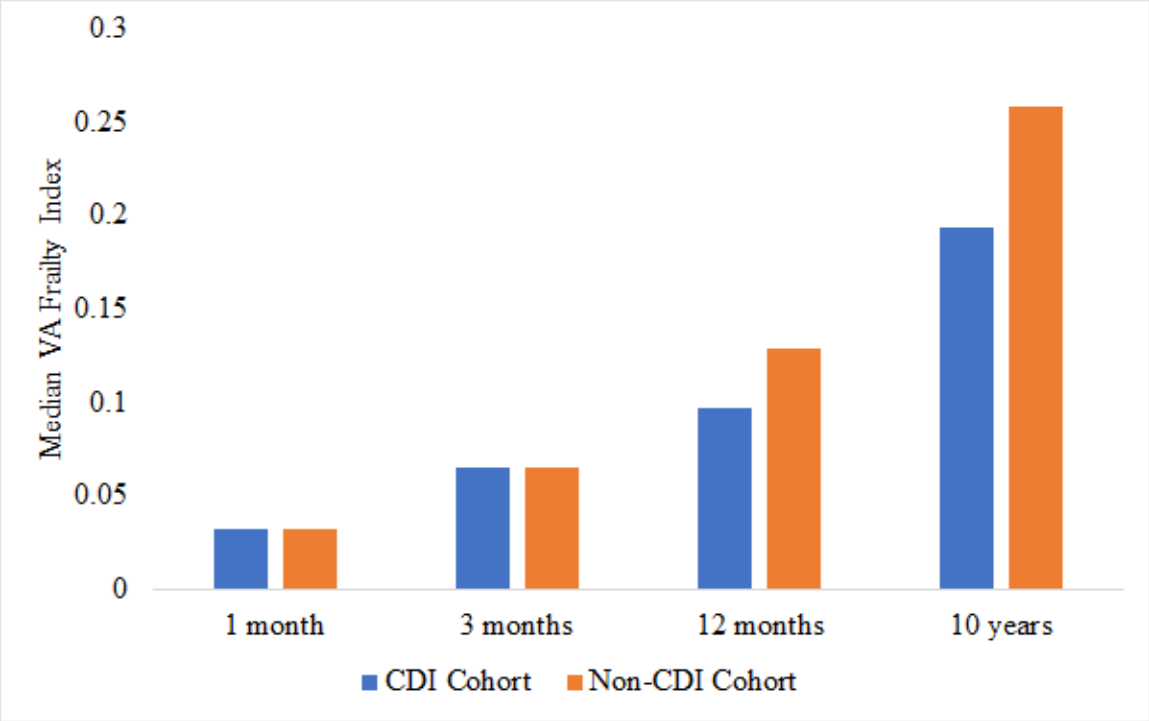
Fractures	125 (1.6%)	150 (1.6%)	0.7391	0.86 (0.62-1.18)	0.91 (0.68-1.22)
12 months	**n=7203**	**n=9013**			
Any frailty condition	1928 (26.8%)	2121 (23.5%)	<0.0001	1.19 (1.11-1.28)	1.27 (1.15-1.41)[c]
Coagulopathy	130 (1.8%)	118 (1.3%)	0.0109	1.38 (1.08-1.78)	1.84 (1.33-2.54)[c]
Weight loss	304 (4.2%)	277 (3.1%)	<0.0001	1.39 (1.18-1.64)	1.42 (1.14-1.77)[c]
Fluid & electrolyte imbalance	29 (0.4%)	28 (0.3%)	0.3273	1.30 (0.77-2.18)	1.41 (0.65-3.03)
Anemia	1313 (18.2%)	1390 (15.4%)	<0.0001	1.22 (1.13-1.33)	1.15 (1.02-1.29)[b]
Falls	176 (2.4%)	224 (2.5%)	0.8643	0.98 (0.80-1.20)	1.01 (0.77-1.32)
Fractures	280 (3.9%)	390 (4.3%)	0.1611	0.89 (0.76-1.05)	1.05 (0.85-1.29)

[a]1 month and 3 month covariates included: bacteremia, pneumonia, skin infection, endocarditis, UTI, device infection, ART, shock, sepsis, perforated intestine, ileus, megacolon, acute renal failure, concomitant antibiotics, concomitant gastric acid suppressants, WBC, CRP, albumin, SCr, concomitant opioids, concomitant anti-diarrheals, concomitant laxatives, ICU stay, hospital length of stay. 12 month covariates included 1 and 3 month covariates plus the following assessed during 12 months of follow-up: hypertension, dyslipidemia, irritable bowel disease, irritable bowel syndrome, obesity, GERD, transplant, schizophrenia, depression, bipolar, anxiety, PTSD, alcohol abuse, myocardial infarction, CHF, peripheral vascular disease, cerebral vascular disease, dementia, COPD, rheumatic disease, any liver disease, diabetes w/ and w/o complications, hemi/paraplegia, HIV/AIDS, any antibiotics (including high risk), in/outpatient visits, dialysis, LTCF stay.
[b]Adjusted p>0.0001
[c]Adjusted p<0.0001

Next, we calculated the median VA frailty index score for each cohort at each follow-up period after excluding those who died at each follow-up period. The median frailty index was the same in each cohort at 1 month (0.032) and 3 months (0.065), but then

was lower among CDI patients compared to controls at 12 months (0.097 vs. 0.129, p<0.0001) and 10 years (0.194 vs. 0.258, p<0.0001) (Figure 5.4).

Figure 5.4. Median VA frailty index over time among surviving CDI and non-CDI patients

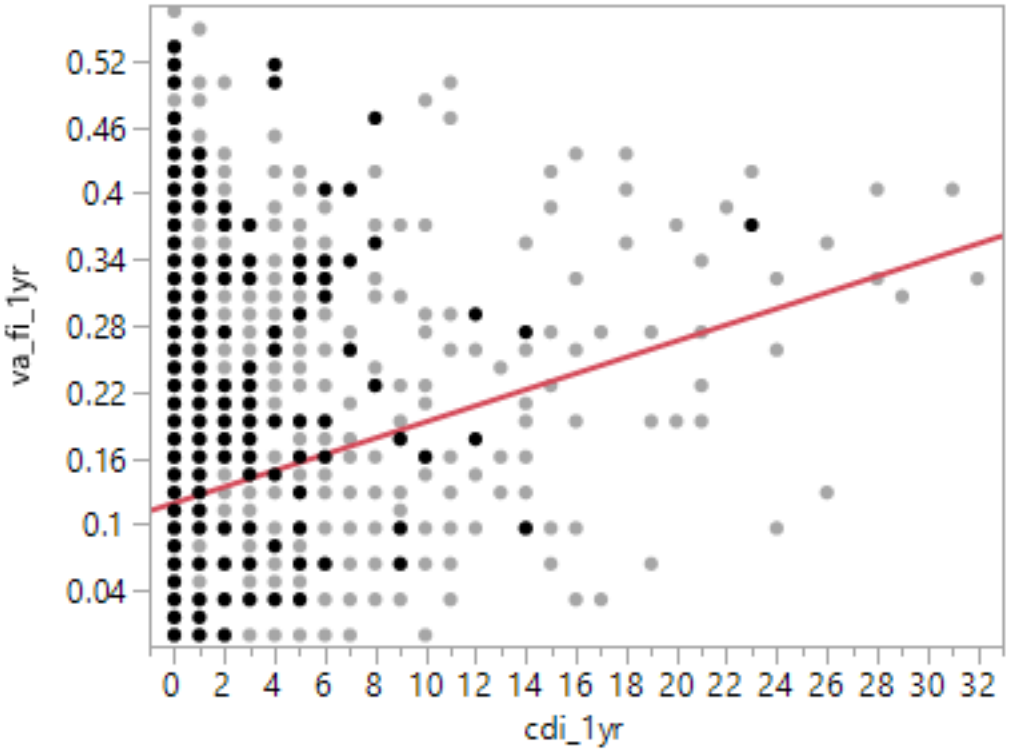


Additionally, we evaluated the association between baseline VA frailty index and mortality in both cohorts using the original unmatched cohorts. Median baseline VA frailty index was significantly higher among those who died within 30 days compared to those who did not (0.161 vs. 0.113, p<0.0001). Similar findings were seen for those who died within 90 days (0.161 vs. 0.097, p<0.0001), and 12 months (0.161 vs. 0.097, p<0.0001).

Finally, to determine the potential "dose-response" relationship between CDI and frailty, we assessed the correlation between the number of CDI episodes during follow-up

at 12 months and the VA frailty index at 12 months. Number of CDI episodes was positively and significantly correlated with VA frailty index ($p<0.0001$), though little of the variability in the VA frailty index could be attributed to the number of CDI episodes ($R^2=0.0250$) (Figure 5.5). We also assessed the relationship between the number of CDI episodes and the development of any frailty-associated condition at 1 year and found a significant positive association ($p<0.0001$).

Figure 5.5. Correlation between CDI episodes and VA frailty index during 12-month follow-up



SPECIFIC AIM 2: DEFINE THE LONG-TERM IMPACT OF CDI ON HEALTHY AGING IN A NATIONAL RETROSPECTIVE VETERAN COHORT

Hypothesis 2.1: CDI patients will experience earlier mortality over a 10-year follow-up period compared to non-CDI controls

For analyses of long-term health outcomes, all-cause mortality, aging-related conditions, and frailty-associated conditions were assessed at a 10-year follow up for all patients who had ten years of data available (i.e., those with an index encounter between fiscal year 2003 and 2008). To assess all-cause mortality at ten years, we excluded a total of 23,106 (77.4%) patients from the unmatched cohorts (11,472 CDI and 11,634 controls) who did not have ten years of follow up (excluded patients after 2008 fiscal year). Following propensity score matching, there were a total of 3,464 CDI patients and 3,302 control patients (6,766 patients total) for analyses. CDI and control patients were well-matched in regard to baseline demographics, prior healthcare exposures, prior medication exposures, and prior comorbidities.

All-cause mortality was statistically higher among CDI patients at the 10-year follow up when compared to non-CDI controls (69.1% vs. 40.6%, $p<0.0001$). Risk of mortality at 10-year follow up was 1.62 times higher in those with CDI after adjusting for covariates (Table 5.8). A 10-year survival analysis was performed for all-cause mortality, excluding patients who died during the encounter (0 days to death), and shows a

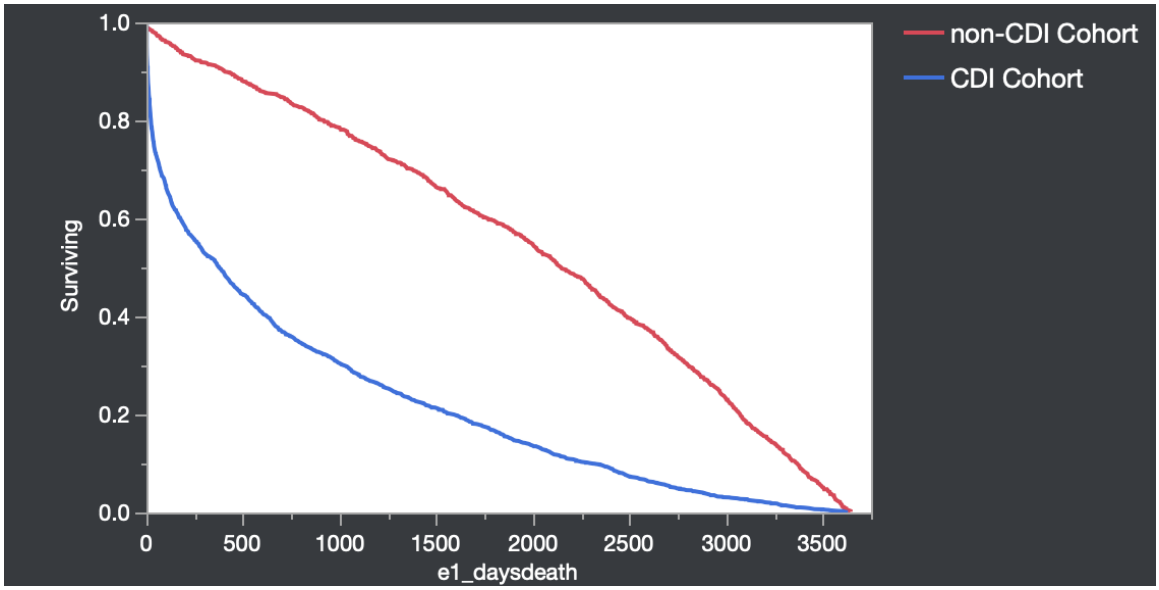
statistically significant difference in time (days) to death in CDI patients compared to non-CDI controls (p<0.0001) (Figure 5.6).

Table 5.8. Prevalence of mortality at 10-year follow-up

	CDI Cohort (n=3464)	Non-CDI Cohort (n=3302)	P-value	OR (99% CI)	Adjusted OR (99% CI)[a]
Mortality	2394 (69.1%)	1339 (40.6%)	<0.0001	3.28 (2.97-3.63)	1.62 (1.34-1.97)[b]

[a]10 year covariates included: bacteremia, pneumonia, skin infection, endocarditis, UTI, device infection, ART, shock, sepsis, perforated intestine, ileus, megacolon, acute renal failure, concomitant antibiotics, concomitant gastric acid suppressants, WBC, CRP, albumin, SCr, concomitant opioids, concomitant anti-diarrheals, concomitant laxatives, ICU stay, hospital length of stay and the following assessed during 10 years of follow-up: hypertension, dyslipidemia, irritable bowel disease, irritable bowel syndrome, obesity, GERD, transplant, schizophrenia, depression, bipolar, anxiety, PTSD, alcohol abuse, myocardial infarction, CHF, peripheral vascular disease, cerebral vascular disease, dementia, COPD, rheumatic disease, any liver disease, diabetes w/ and w/o complications, hemi/paraplegia, HIV/AIDS, any antibiotics (including high risk), in/outpatient visits, dialysis, LTCF stay.
[b]p<0.0001

Figure 5.6. Kaplan Meier survival curve for mortality at 10 years.



Hypothesis 2.2: CDI patients will experience more aging-related conditions over a 10-year follow-up period compared to non-CDI controls

For 10-year aging-related condition analyses, we excluded a total of 14,698 patients without 10-year follow-up and an additional 2,078 patients who died within that 10-year period leaving 2,174 patients (794 CDI and 1,380 control patients) for analyses. At 10 years, CDI patients had numerically fewer aging-related condition (40.3% vs. 52.3%, $p<0.0001$) though this comparison did not remain significantly different after adjustment for covariates (OR 1.13, 99% CI 0.52-2.46) (Table 5.9). Individual aging-related conditions were each numerically lower in the CDI cohort, though none reached statistical significance after adjustment for covariates. Other significant predictors of aging-related conditions at 10 years included: hypertension at 10 years (OR 2.30, 99% CI 1.64-3.23) and peripheral vascular diseases (OR 2.00, 99% CI 1.58-2.54). Among CDI patients only, the number of CDI episodes and the development of aging-related conditions at 10 year were positively associated but did not reach statistical significance ($p=0.0015$).

Table 5.9. Prevalence of aging-related conditions at 10-year follow-up

	CDI Cohort (n=794)	Non-CDI Cohort (n=1380)	P-value	OR (99% CI)	Adjusted OR (99% CI)[a]
Any aging condition	320 (40.3%)	722 (52.3%)	<0.0001	0.62 (0.52-0.73)	1.03 (0.76-1.39)
Cardiovascular disease	176 (22.2%)	466 (33.8%)	<0.0001	0.56 (0.46-0.68)	0.98 (0.71-1.37)
Cancer	153 (19.3%)	306 (22.2%)	0.1084	0.84 (0.67-1.04)	1.14 (0.81-1.61)
Neurodegenerative disease	95 (12.0%)	196 (14.2%)	0.1373	0.82 (0.63-1.07)	1.27 (0.83-1.97)

[a]10 year covariates included: bacteremia, pneumonia, skin infection, endocarditis, UTI, device infection, ART, shock, sepsis, perforated intestine, ileus, megacolon, acute renal failure, concomitant antibiotics, concomitant gastric acid suppressants, WBC, CRP, albumin, SCr, concomitant opioids, concomitant anti-diarrheals, concomitant laxatives, ICU stay, hospital length of stay and the following assessed during 10 years of follow-up: hypertension, dyslipidemia, irritable bowel disease, irritable bowel syndrome, obesity, GERD, transplant, schizophrenia, depression, bipolar, anxiety, PTSD, alcohol abuse, CHF, peripheral vascular disease, COPD, rheumatic disease, any liver disease, diabetes w/ and w/o complications, hemi/paraplegia, HIV/AIDS, any antibiotics (including high risk), in/outpatient visits, dialysis, LTCF stay.

Hypothesis 2.3: CDI patients will experience more frailty-associated diagnoses over a 10-year follow-up period compared to non-CDI controls

For 10-year frailty-associated condition analyses, we excluded a total of 14,569 patients without 10-year follow-up and an additional 2,247 patients who died within that 10-year period leaving 2,182 patients (761 CDI and 1,421 control patients) for analyses. At 10 years, CDI patients had numerically fewer aging-related condition (55.5% vs. 70.4%, $p<0.0001$) though this comparison did not remain significantly different after adjustment for covariates (OR 1.22, 99% CI 0.87-1.72) (Table 5.10). Most individual frailty-associated conditions were each numerically lower in the CDI cohort, though none reached statistical significance after adjustment for covariates. Other significant predictors of frailty-associated conditions at 10 years included: antibiotic use within 10 years (OR 3.40, 99% CI 1.94-5.96), dementia at 10 years (OR 2.57, 99% CI 1.56-4.26), and renal disease at 10 years (OR 2.01, 99% CI 1.46-2.78).

Table 5.10. Prevalence of frailty-associated conditions at 10-year follow-up

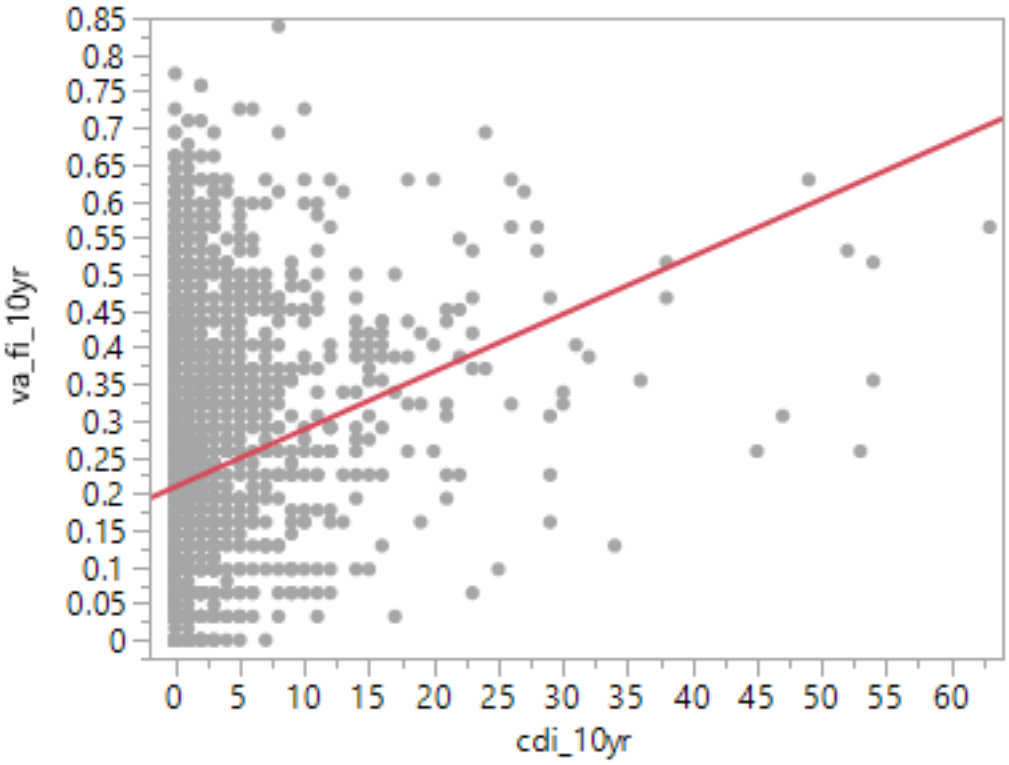
	CDI Cohort (n=761)	Non-CDI Cohort (n=1,421)	P-value	OR (99% CI)	Adjusted OR (99% CI)[+]
Any frailty condition	422 (55.4%)	1001 (70.4%)	<0.0001	0.52 (0.44-0.63)	1.20 (0.85-1.69)
Coagulopathy	54 (7.1%)	95 (6.7%)	0.7179	1.07 (0.75-1.51)	2.38 (1.36-4.16)
Weight loss	97 (12.7%)	244 (17.2%)	0.0060	0.70 (0.55-.91)	1.03 (0.69-1.55)
Fluid & electrolyte imbalance	10 (1.3%)	26 (1.8%)	0.3589	0.71 (0.34-1.49)	0.77 (0.17-3.54)
Anemia	275 (36.1%)	713 (50.2%)	<0.0001	0.56 (0.47-0.67)	0.89 (0.65-1.22)
Falls	66 (8.7%)	225 (15.8%)	<0.0001	0.50 (0.38-0.67)	0.53 (0.33-0.85)
Fractures	157 (20.6%)	390 (27.4%)	0.0004	0.69 (0.56-0.85)	1.15 (0.82-1.61)

[a]10 year covariates included: bacteremia, pneumonia, skin infection, endocarditis, UTI, device infection, ART, shock, sepsis, perforated intestine, ileus, megacolon, acute renal failure, concomitant antibiotics, concomitant gastric acid suppressants, WBC, CRP, albumin, SCr, concomitant opioids, concomitant anti-diarrheals, concomitant laxatives, ICU stay, hospital length of stay and the following assessed during 10 years of follow-up: hypertension, dyslipidemia, irritable bowel disease, irritable bowel syndrome, obesity, GERD, transplant, schizophrenia, depression, bipolar, anxiety, PTSD, alcohol abuse, myocardial infarction, CHF, peripheral vascular disease, cerebral vascular disease, dementia, COPD, rheumatic disease, any liver disease, diabetes w/ and w/o complications, hemi/paraplegia, HIV/AIDS, any antibiotics (including high risk), in/outpatient visits, dialysis, LTCF stay.

Finally, we assessed the correlation between the number of CDI episodes during follow-up at 10 years and the VA frailty index at 10 years. Number of CDI episodes was positively and significantly correlated with VA frailty index ($p<0.0001$), though little of the variability in the VA frailty index could be attributed to the number of CDI episodes ($R^2=0.0269$) (Figure 5.7). We also assessed the relationship between the number of CDI

episodes and the development of any frailty-associated condition at 10 years and found a significant positive association ($p<0.0001$). Number of CDI episodes was also associated with individual frailty conditions at 10 years, including coagulopathy, involuntary weight loss, anemia, and falls ($p<0.0001$ for all).

Figure 5.7. Correlation between CDI episodes and VA frailty index during 10-year follow-up



SUBGROUP ANALYSES: FEMALE-ONLY

Given that the VHA population is predominantly male, we conducted a subgroup analysis on female veterans only to assess the generalizability of our overall findings to females. Cohorts that were previously propensity score matched for mortality, aging, and frailty analyses were limited to female patients only. Table 5.11 presents the findings of the short and long-term outcomes.

Among females included in the study, CDI patients experienced significantly higher mortality compared to control patients and the risk after adjustment for covariates was highest early in the follow-up period (1 month OR 4.23, 99% CI 1.41-12.68) compared to 3-month and 12-month follow-ups. Interestingly, mortality was numerically lower among CDI patients at 10 years, though there were notably few patients available for the full 10-year follow-up resulting in imprecision in risk estimates (i.e., wide confidence intervals in multivariable models). Overall, mortality rates were much lower among this female subgroup compared to the overall population that was approximately 94% male. For example, at 12 months, mortality among the CDI cohorts was lower among females compared to the overall cohort (11.6% vs. 27.7%) and lower among control females compared to overall controls (3.3% vs. 7.6%).

Analyses of aging-related conditions among females yielded similar results to overall findings: there was no significant difference in the development of aging-related conditions during short- or long-term follow-up. Similar to mortality, aging-related conditions were lower among females compared to males. For example, the development

of any aging-related condition at 12 months was lower among CDI females compared to the overall CDI cohort (8.6% vs. 15.6%).

Frailty analyses for females were somewhat different than the overall cohort. While frailty conditions were numerically lower, albeit by a smaller absolute percentage difference, the comparisons did not reach statistical significance for 1-month, 3-month, 12-month, and 10 year follow-up periods. Similar to mortality, frailty-associated conditions were lower among females compared to males. For example, the development of any frailty-associated condition at 12 months was lower among CDI females compared to the overall CDI cohort (22.1% vs. 26.8%).

Table 5.11. Prevalence of aging- and frailty-associated conditions and mortality at follow-up among female patients only

	CDI Cohort	Non-CDI Cohort	P-value	OR (99% CI)	Adjusted OR (99% CI)[a]
Mortality					
	n=742	**n=763**			
1 month	42 (5.7%)	5 (0.7%)	<0.0001	9.10 (3.58-23.13)	4.23 (1.41-12.68)[c]
3 months	58 (7.8%)	13 (1.7%)	<0.0001	4.89 (2.66-9.01)	2.50 (1.16-5.37)[c]
12 months	86 (11.6%)	25 (3.3%)	<0.0001	3.87 (2.45-6.12)	1.48 (0.73-3.00)
	n=105	**n=182**			
10 years	60 (57.1%)	145 (79.7%)	<0.0001	2.94 (1.73-4.99)	2.58 (0.18-38.03)

Table 5.11, *cont.*

Aging-related conditions					
1 month	**n=548**	**n=573**			
Any aging condition	18 (3.3%)	19 (3.3%)	0.9767	0.99 (0.51-1.91)	0.89 (0.36-2.17)
Cardiovascular disease	4 (0.7%)	7 (1.2%)	0.4004	0.59 (0.17-2.04)	0.94 (0.16-5.69)
Cancer	15 (2.7%)	10 (1.7%)	0.2597	1.58 (0.71-3.56)	1.23 (0.41-3.71)
Neurodegenerative diseases	0 (0.0%)	2 (0.3%)	0.1011	--	--
3 months	**n=540**	**n=569**			
Any aging condition	22 (4.1%)	28 (4.9%)	0.4963	0.82 (0.46-1.45)	0.68 (0.29-1.58)
Cardiovascular disease	6 (1.1%)	12 (2.1%)	0.1840	0.52 (0.19-1.40)	0.54 (0.10-2.81)
Cancer	17 (3.1%)	14 (2.5%)	0.4873	1.29 (0.63-2.64)	1.25 (0.44-3.55)
Neurodegenerative diseases	1 (0.2%)	2 (0.4%)	0.5900	0.53 (0.05-5.82)	--
12 months	**n=525**	**n=561**			
Any aging condition	45 (8.6%)	69 (12.3%)	0.0443	0.67 (0.45-0.99)	0.40 (0.17-0.93)[b]
Cardiovascular disease	19 (3.6%)	36 (6.4%)	0.0339	0.55 (0.31-0.97)	0.78 (0.27-2.38)
Cancer	20 (3.8%)	23 (4.1%)	0.8062	0.93 (0.50-1.71)	0.78 (0.28-2.17)
Neurodegenerative diseases	11 (2.1%)	13 (2.3%)	0.8034	0.90 (0.40-2.03)	0.89 (0.15-5.18)
10 years	**n=49**	**n=102**			
Any aging condition	20(40.8%)	47(46.1%)	0.5416	0.81 (0.40-1.61)	2.75 (0.48-15.60)
Cardiovascular disease	12(24.5%)	27(26.5%)	0.7940	0.90 (0.41-1.98)	0.60 (0.03-13.92)
Cancer	11(22.4%)	17(16.7%)	0.3978	1.45 (0.62-3.38)	16.45 (1.25-216.29)

Table 5.11, *cont.*

Neurodegenerative diseases	4 (8.2%)	9 (8.8%)	0.6617	0.92 (0.27-3.14)	--
Frailty-associated conditions					
1 month	**n=513**	**n=559**			
Any frailty condition	39 (7.6%)	25(4.5%)	0.0304	1.76 (1.05-2.95)	0.98 (0.53-1.60)
Coagulopathy	4 (0.8%)	3 (0.5%)	0.4530	1.46 (0.32-6.53)	1.40 (0.23-8.53)
Weight loss	4 (0.8%)	2 (0.4%)	0.3039	2.19 (0.40-12.00)	--
Fluid & electrolyte imbalance	1 (0.2%)	0 (0.0%)	0.4785	--	--
Anemia	31 (6.0%)	16(2.9%)	0.0082	2.18 (1.18-4.04)	1.14 (0.54-2.39)
Falls	2 (0.4%)	4 (0.7%)	0.8699	0.54 (0.10-2.98)	--
Fractures	3 (0.6%)	3 (0.5%)	0.6156	1.09 (0.22-5.42)	1.05 (0.14-7.93)
3 months	**n=504**	**n=556**			
Any frailty condition	59(11.7%)	55(9.9%)	0.3413	1.22 (0.83-1.79)	0.83 (0.50-1.37)
Coagulopathy	3 (0.6%)	6 (1.1%)	0.8846	0.55 (0.14-2.21)	1.02 (0.19-5.49)
Weight loss	8 (1.6%)	4 (0.7%)	0.1486	2.23 (0.67-7.44)	0.98 (0.19-4.84)
Fluid & electrolyte imbalance	1 (0.2%)	0 (0.0%)	0.4755	--	--
Anemia	42 (8.3%)	36(6.5%)	0.1493	1.31 (0.83-2.09)	0.84 (0.46-1.53)
Falls	5 (1.0%)	4 (0.7%)	0.6292	1.38 (0.37-5.18)	0.16 (0.02-1.63)
Fractures	7 (1.4%)	8 (1.4%)	0.6269	0.96 (0.35-2.68)	1.09 (0.29-4.17)

Table 5.11, *cont.*

12 months	**n=488**	**n=551**			
Any frailty condition	108(22.1%)	128(23.2%)	0.6728	0.93 (0.70-1.26)	1.28 (0.79-2.07)
Coagulopathy	4 (0.8%)	8 (1.5%)	0.8943	0.56 (0.17-1.87)	--
Weight loss	18 (3.7%)	13 (2.4%)	0.2090	1.58 (0.77-3.27)	1.14 (0.32-4.03)
Fluid & electrolyte imbalance	3 (0.6%)	2 (0.4%)	0.4432	1.69 (0.28-10.20)	--
Anemia	65 (13.3%)	77 (14.0%)	0.7590	0.95 (0.66-1.35)	1.09 (0.63-1.89)
Falls	12 (2.5%)	14 (2.5%)	0.9328	0.97 (0.44-2.11)	0.51 (0.07-3.49)
Fractures	17 (3.5%)	23 (4.2%)	0.5627	0.83 (0.44-1.57)	3.75 (1.16-12.12)[b]
10 years	**n=50**	**n=95**			
Any frailty condition	32 (64.0%)	72 (75.8%)	0.1379	0.57 (0.27-1.19)	--
Coagulopathy	3 (6.0%)	6 (6.3%)	0.6570	0.95 (0.23-3.96)	--
Weight loss	6 (12.0%)	20 (21.1%)	0.9463	0.51 (0.19-1.37)	--
Fluid & electrolyte imbalance	0 (0.0%)	0 (0.0%)	1.0000	--	--
Anemia	15 (30.0%)	52 (54.7%)	0.0041	0.35 (0.17-0.73)	--
Falls	6 (12.0%)	15 (15.8%)	0.8047	0.73 (0.26-2,01)	--
Fractures	20 (40.0%)	34 (35.8%)	0.6189	1.19 (0.59-2.42)	--

[a]1 month and 3 month covariates included: bacteremia, pneumonia, skin infection, endocarditis, UTI, device infection, ART, shock, sepsis, perforated intestine, ileus, megacolon, acute renal failure, concomitant antibiotics, concomitant gastric acid suppressants, WBC, CRP, albumin, SCr, concomitant opioids, concomitant anti-diarrheals, concomitant laxatives, ICU stay, hospital length of stay. 12 month and 10 year covariates included 1 and 3 month covariates plus the following assessed during 12 months or 10 years of follow-up: hypertension, dyslipidemia, irritable bowel disease, irritable bowel syndrome, obesity, GERD, transplant, schizophrenia, depression, bipolar, anxiety, PTSD, alcohol abuse, CHF, peripheral vascular disease, COPD, rheumatic disease, any liver disease, diabetes w/ and w/o complications, hemi/paraplegia, HIV/AIDS, any antibiotics (including high risk), in/outpatient visits, dialysis, LTCF stay.
[b]Adjusted $p>0.0001$
[c]Adjusted $p<0.0001$

SUBGROUP ANALYSES: COMMUNITY-ONSET CDI ONLY

CDI has traditionally been classified based on the setting on onset to assist healthcare providers with infection surveillance. CDI may be classified as community- or hospital-onset and also as healthcare facility-associated or not associated. Given that patients who develop CDI in the community may differ with respect to risk factors, presentation, and underlying conditions, and risk for poor outcomes we conducted a subgroup analysis on community-onset CDI (CO-CDI) veterans only to assess the generalizability of our overall findings to community-onset CDI only. The original CDI cohort was limited to community-onset CDI patients only (CO-HCFA-CDI and CA-CDI), then new propensity score matched cohorts were created as described previously for mortality, aging, and frailty analyses. Table 5.12 presents the findings of the short and long-term outcomes.

Among patients included in these subgroup analyses, CDI patients experienced significantly higher mortality at each follow-up compared to control patients and the risk after adjustment for covariates was highest early in the follow-up period (1 month OR 2.99, 99% CI 2.49-3.59) compared to 3-month, 12-month, and 10-year follow-ups. Overall, mortality rates were lower among this CO-CDI subgroup compared to the overall population. For example, at 12 months, mortality among the CDI cohorts was lower among CO-CDI patients compared to the overall cohort (23.7% vs. 27.7%). Specifically, mortality was lowest for patients with CA-CDI (19.0%), followed by CO-HCFA-CDI (27.6%), and HCFO-CDI (27.7%). This is likely due to lower rates of comorbidities and complications between these groups. The median baseline Charlson

comorbidity score was 1, 2, and 2, respectively in these groups. Common severity indicators were also least common among CA-CDI patients: sepsis 14.0%, 19.7%, 18.1% and acute renal failure 24.2%, 30.8%, 31.0%, respectively.

Analyses of aging-related conditions among CO-CDI patients yielded similar results to overall findings: there was no significant difference in the development of aging-related conditions during short- or long-term follow-up. Similar to mortality, aging-related conditions were lower among CO-CDI patients compared to the overall cohort. For example, the development of any aging-related condition at 12 months was lower among CO-CDI patients compared to the overall CDI cohort (13.3% vs. 15.6%), though this difference was not as pronounced as we saw in the female subgroup analyses.

Frailty analyses for CO-CDI patients demonstrated numerically somewhat higher rates of frailty-associated conditions at 1 month, 3 months, and 12 months, but lower rates at 10 years. None of these comparisons reached statistical significance though, unlike overall analyses that include HO-CDI patients. Frailty-associated conditions were only slightly lower among CO-CDI patients compared to the overall cohort. For example, the development of any frailty-associated condition at 12 months was 25.1% in the CO-CDI subgroup compared to 26.8% in the overall CDI cohort (22.1%).

Table 5.12. Prevalence of mortality, aging-, and frailty-associated conditions at follow-up among patients with community-onset CDI only

	CDI Cohort (n=9338)	Non-CDI Cohort (n=9338)	P-value	OR (99% CI)	Adjusted OR (99% CI)[a]
Mortality					
1 month	1002(10.7%)	207 (2.2%)	<0.0001	5.30 (4.55-6.18)	2.99 (2.49-3.59)[c]
3 months	1250(13.4%)	305 (3.3%)	<0.0001	4.18 (3.72-4.70)	2.44 (2.12-2.81)[c]
12 months	2211(23.7%)	770 (8.3%)	<0.0001	3.45 (3.16-3.77)	1.87 (1.65-2.11)[c]
	n=1661	**n=1555**			
10 years	1089(65.6%)	665 (47.8%)	<0.0001	2.54 (2.21-2.94)	1.35 (1.01-1.80)[b]
Aging-related conditions					
1 month	**n=5,280**	**n=5704**			
Any aging condition	271 (5.1%)	265 (4.6%)	0.2370	1.11 (0.93-1.32)	0.80 (0.65-1.00)
Cardiovascular disease	101 (1.9%)	105 (1.8%)	0.7809	1.04 (0.79-1.37)	0.88 (0.62-1.24)
Cancer	143 (2.7%)	145 (2.5%)	0.5860	1.07 (0.84-1.35)	0.69 (0.52-0.92)[b]
Neurodegenerative diseases	44 (0.8%)	26 (0.5%)	0.0127	1.84 (1.13-2.98)	1.48 (0.81-2.71)
3 months	**n=5100**	**n=5645**			
Any aging condition	411 (8.1%)	458 (8.1%)	0.9175	0.99 (0.86-1.14)	0.81 (0.68-0.96)[b]
Cardiovascular disease	151 (3.0%)	214 (3.8%)	0.0173	0.77 (0.63-0.96)	0.68 (0.52-0.89)[b]

Table 5.12, *cont.*

Cancer	218(4.3%)	220(3.9%)	0.3237	1.10 (0.91-1.33)	0.81 (0.64-1.03)
Neurodegenerative diseases	75 (1.5%)	55 (1.0%)	0.0188	1.52 (1.07-2.15)	1.68 (1.07-2.63)[b]
12 months	**n=4714**	**n=5476**			
Any aging condition	628(13.3%)	808(14.8%)	0.0379	0.89 (0.79-0.99)	1.02 (0.84-1.23)
Cardiovascular disease	308 (6.5%)	447 (8.2%)	0.0017	0.89 (0.68-0.91)	0.87 (0.55-1.36)
Cancer	254 (5.4%)	295 (5.4%)	0.9981	1.00 (0.84-1.19)	1.02 (0.82-1.28)
Neurodegenerative diseases	136 (2.9%)	143 (2.6%)	0.3992	1.11 (0.87-1.41)	1.45 (1.01-2.08)
10 years	**n=396**	**n=599**			
Any aging condition	159(40.2%)	317(52.9%)	<0.0001	0.60 (0.46-0.77)	2.12 (0.70-6.36)
Cardiovascular disease	91 (23.0%)	191(31.9%)	0.0021	0.64 (0.48-0.85)	1.07 (0.20-5.64)
Cancer	81 (20.5%)	152(25.4%)	0.0711	0.76 (0.56-1.03)	1.07 (0.63-1.81)
Neurodegenerative diseases	52 (13.1%)	84 (14.0%)	0.6879	0.93 (0.64-1.34)	1.52 (0.68-3.41)
Frailty-associated conditions					
1 month	**n=5163**	**n=5570**			
Any frailty condition	398 (7.7%)	349 (6.3%)	0.0033	1.25 (1.08-1.45)	0.81 (0.68-0.97)
Coagulopathy	22 (0.4%)	21 (0.4%)	0.6876	1.13 (0.62-2.06)	0.93 (0.47-1.84)
Weight loss	70 (1.4%)	29 (0.5%)	<0.0001	2.63 (1.70-4.06)	1.98 (1.19-3.29)[b]

Table 5.12, *cont.*

Fluid & electrolyte imbalance	6 (0.1%)	3 (0.1%)	0.2179	2.16 (0.54-8.64)	1.96 (0.42-9.21)
Anemia	288 (5.6%)	241 (4.3%)	0.0028	1.31 (1.09-1.56)	0.74 (0.59-0.92)[b]
Falls	26 (0.5%)	26 (0.5%)	0.7839	1.08 (0.63-1.86)	0.94 (0.49-1.79)
Fractures	26 (0.5%)	61 (1.1%)	0.0005	0.46 (0.29-0.72)	0.48 (0.28-0.82)[b]
3 months	**n=4986**	**n=5499**			
Any frailty condition	696(14.0%)	600(10.9%)	<0.0001	1.32 (1.18-1.49)	0.91 (0.78-1.05)
Coagulopathy	38 (0.8%)	32 (0.6%)	0.2581	1.31 (0.82-2.10)	1.02 (0.58-1.79)
Weight loss	125 (2.5%)	60 (1.1%)	<0.0001	2.33 (1.71-3.18)	1.48 (1.03-2.12)[b]
Fluid & electrolyte imbalance	8 (0.2%)	6 (0.1%)	0.3255	1.47 (0.51-4.24)	2.19 (0.58-8.31)
Anemia	485 (9.7%)	411 (7.5%)	<0.0001	1.33 (1.16-1.53)	0.85 (0.72-1.01)
Falls	50 (1.0%)	47 (0.9%)	0.4292	1.18 (0.79-1.75)	1.04 (0.63-1.71)
Fractures	62 (1.2%)	101 (1.8%)	0.0136	0.67 (0.49-0.93)	0.65 (0.45-0.95)[b]
12 months	**n=4581**	**n=5330**			
Any frailty condition	1148 (25.1%)	1251 (23.5%)	0.0657	1.09 (0.99-1.19)	1.18 (1.03-1.35)[b]
Coagulopathy	69 (1.5%)	79 (1.5%)	0.9216	1.02 (0.73-1.41)	1.27 (0.83-1.93)
Weight loss	190 (4.2%)	155 (2.9%)	0.0008	1.44 (1.16-1.79)	1.52 (1.13-2.04)[b]

Table 5.12, *cont.*

Fluid & electrolyte imbalance	15 (0.3%)	18 (0.3%)	0.9294	0.97 (0.49-1.93)	1.94 (0.64-5.88)
Anemia	771(16.8%)	772(14.5%)	0.0013	1.19 (1.07-1.33)	1.16 (0.99-1.36)
Falls	108 (2.4%)	139 (2.6%)	0.4248	0.90 (0.69-1.16)	0.93 (0.66-1.32)
Fractures	164 (3.6%)	238 (4.5%)	0.0254	0.79 (0.65-0.97)	0.95 (0.72-1.24)
10 years	**n=391**	**n=647**			
Any frailty condition	213(54.5%)	459(70.9%)	<0.0001	0.49 (0.38-0.64)	1.21 (0.72-2.05)
Coagulopathy	26 (6.7%)	50 (7.8%)	0.5156	0.85 (0.52-1.39)	1.67 (0.75-3.69)
Weight loss	63 (16.1%)	117(18.1%)	0.4145	0.87 (0.62-1.22)	1.39 (0.78-2.49)
Fluid & electrolyte imbalance	5 (1.3%)	14 (2.2%)	0.9008	0.59 (0.21-1.64)	--
Anemia	147(37.6%)	307(47.5%)	0.0019	0.68 (0.52-0.86)	0.97 (0.61-1.55)
Falls	32 (8.2%)	101(15.6%)	0.0004	0.48 (0.32-0.73)	0.64 (0.31-1.32)
Fractures	83 (21.2%)	176(27.2%)	0.0298	0.72 (0.54-0.97)	1.00 (0.61-1.64)

[a]1 month and 3 month covariates included: bacteremia, pneumonia, skin infection, endocarditis, UTI, device infection, ART, shock, sepsis, perforated intestine, ileus, megacolon, acute renal failure, concomitant antibiotics, concomitant gastric acid suppressants, WBC, CRP, albumin, SCr, concomitant opioids, concomitant anti-diarrheals, concomitant laxatives, ICU stay, hospital length of stay. 12 month and 10 year covariates included 1 and 3 month covariates plus the following assessed during 12 months or 10 years of follow-up: hypertension, dyslipidemia, irritable bowel disease, irritable bowel syndrome, obesity, GERD, transplant, schizophrenia, depression, bipolar, anxiety, PTSD, alcohol abuse, CHF, peripheral vascular disease, COPD, rheumatic disease, any liver disease, diabetes w/ and w/o complications, hemi/paraplegia, HIV/AIDS, any antibiotics (including high risk), in/outpatient visits, dialysis, LTCF stay.
[b]Adjusted p>0.0001
[c]Adjusted p<0.0001

Chapter 6: Discussion

CDI has been previously associated with poor health outcomes, including serious clinical signs/symptoms (e.g., frequent diarrhea leading to dehydration and electrolyte imbalances) and severe complications (e.g., sepsis, megacolon). Importantly, CDI is often preceded by disruption of the normal host gut microbiome, which can persist following the episode and lead to future recurrent CDI episodes and possibly risk for other microbiome-mediated conditions. Due to these effects, we evaluated the primary outcome of all-cause mortality in CDI patients compared to non-CDI controls in a national study of U.S. veterans. We then investigated risk for the development of secondary outcomes, including aging-related and frailty-associated conditions, in the same patient population. This is one of the first studies to evaluate long-term mortality rates in a CDI population and risk for non-infectious microbiome-mediated conditions. Overall, we found that CDI was associated with a significant increase in mortality in the short-term and long-term. CDI was also associated with short-term development of frailty-associated conditions, especially weight loss and anemia, but not chronic aging-related conditions.

ALL-CAUSE MORTALITY OUTCOMES

All-cause mortality was common among CDI patients; more than one-quarter of CDI patients died within one year of the index episode compared to only 7.6% in the control group. Mortality risk was significantly higher among CDI patients at all three short-term follow-up periods (1-, 3-, and 12-months), with increased risk ranging from 2.7 (at 12 months) to nearly 3.8 (at 1 month) times higher in CDI patients compared to

non-CDI controls. At the 10-year follow-up, mortality risk was nearly two times higher (OR 1.62) among CDI patients, with survival analyses showing a statistically significant difference in days to death among all of the follow-up time points ($p<0.0001$).

Our findings of increased mortality risk in veterans with CDI is consistent with literature both within the VA patient population and the civilian population.[55,58,59] Mortality rates of CDI patients vary greatly between studies. Research in the VA population has shown mortality in CDI patients to range from 11% to 37% varying by severity,[15,59] while non-VA data has cited higher rates (3%-43%),[60-63] though there may be numerous reasons for these differences. First, more studies exist looking at mortality in the general CDI population as compared to veterans. Additionally, studies of this nature can be affected by the statistical methods used, the time frame in which mortality was assessed, and whether research was conducted during an epidemic or endemic periods of CDI in these populations. As well, European studies show a similar heterogeneity in all-cause mortality in CDI patients (ranging from 4-37%) when compared to US studies.[64] Notably, in our study, we eliminated nearly 80% of the original unmatched CDI population to match with the non-CDI controls; thus, mortality rates reported in our study are likely lower than in the overall VA CDI population.

Here, and in a majority of previous CDI mortality outcome studies, the most pronounced mortality risk was early in the follow-up periods. Higher mortality earlier in the follow up period is not surprising, as the acute symptoms of infection can happen suddenly, quickly escalate, and may compound into serious complications. Specifically, short-term effects of CDI (and the resulting diarrhea) often include severe dehydration,

gastrointestinal inflammation, loss of appetite, and poor nutritional intake and absorption. These symptoms can contribute to more serious complications in a short time frame, such as renal failure, sepsis, and others as previously described, increasing the risk for death earlier in the study period.

Few studies have investigated long-term CDI outcomes, including mortality. Traditionally, CDI studies have defined "long-term" outcomes as those occurring at 1-year post-CDI. There does not appear to be any research investigating long-term outcomes, including mortality, at the 10-year time frame or similar. Some retrospective studies have assessed CDI patients across a 10-year study period but did not have ten years of follow up data on patients as this study did. A recent study in the United Kingdom investigated mortality in CDI patients in the long-term, showing that CDI was associated with a 50% increased risk of death (HR 1.51 (99% CI: 1.05-2.19, p=0.03) at between five to eight years after adjusting for age, sex, the Charlson comorbidity index, malignancies, and nasogastric tube insertion during admission.[65]

Subgroups analyses were performed for two sample populations in this study: females and community-onset CDI (CO-CDI). Our results show female CDI mortality rates are lower than males, though prior literature does not show a consensus in regard to a relationship between sex and mortality outcomes with CDI.[66,67] Female sex has previously been associated with higher CDI incidence;[66-68] this is likely due to exposure to colonized infants, especially through breastfeeding, higher antibiotic prescribing rates, and that females are more likely to seek out medical care.[68] Despite higher rates of infection, females in this study had less than half the mortality rate of males at each short-

term follow-up period and lower mortality at 10 years (57% vs. 69%). In the short-term, these differences could be due to females being more likely to seek medical care earlier in the infection compared to males and to differences in certain mortality predictors compared to males. For example, certain comorbidities (e.g., metastatic cancer, moderate/severe liver disease) and complications (shock, acute renal failure) were less common among females compared to males. The long-term trends follow general longevity sex disparities in the U.S. On average, females live 6-8 years longer than males likely due to biological, social, and behavioral differences.[69]

Community-onset CDI (CO-CDI) was also investigated as subgroup analyses. Similar to the female subgroup, mortality rates were lower in community-onset cases compared to hospital-onset cases. This was driven primarily by CA-CDI patients who had significantly lower mortality rates at 12 months compared to CO-HCFA-CDI and HCFO-CDI. The lower mortality rates among CA-CDI are likely related to the lower prevalence of underlying conditions and less severe infection. Specifically, CA-CDI patients had lower baseline Charlson comorbidity scores and fewer CDI complications.

AGING-RELATED CONDITIONS OUTCOMES

Any aging-related condition and individual aging-related conditions as defined previously were investigated as secondary outcomes of CDI compared to a non-CDI cohort. Bivariable analyses showed no statistically significant differences in the development of aging-related conditions in CDI patients compared to non-CDI controls. Although aging-related conditions were numerically higher in the CDI cohort in the

short-term, the differences were not statistically significant using a p-value cutoff of <0.0001. Regression analysis showed CDI as an independent predictor of cancer diagnosis at 1-month follow up, though this prediction trend was not true at 3- and 12-month follow up. We suspect this association may be due to detection of a malignant condition as a product of infection with *C. difficile*, and not necessarily development of the malignancy due to the infection itself.

Previous literature has focused on the risk of CDI in patient populations already diagnosed with cardiovascular diseases, cancers, and neurodegenerative diseases. Studies have attributed increased CDI risk after cardiac procedures,[70,71] immunosuppression from cancer and accompanying drug therapies,[72] and prolonged hospitalization from multimorbidity.[73] It does not appear that any prior research has investigated the opposite relationship: an increased risk of developing aging-related conditions post-CDI. Though most of this study's findings for aging-relating conditions were not significant, we believe there is cause for further investigation into this area, especially in terms of prospective long-term follow up to determine a stronger potential relationship between CDI and these conditions.

In regard to neurodegenerative conditions specifically, a 2012 study evaluated the host inflammatory response to toxigenic *C. difficile* infection in the rat model, showing that this infection led to increased neuroinflammation (among other types of inflammation).[74] The secretion of neuropeptides as a strong neuroinflammatory response to CDI is important to the discussion of aging-related conditions, as neuroinflammation is a common factor in dementia and other neurodegenerative disorders.[75] Though this study

did not evaluate the long-term effects of neuroinflammation, these data open up the possibility for an association between neurodegenerative disease development post-CDI. Further research should investigate measuring neuroinflammation in the animal, and possibly human, model pre- and post-CDI to prospectively identify neurodegenerative disease risk and development.

We suspect that one of the reasons that CDI patients did not have significantly higher rates of aging-related conditions in the short- or long-term was because of the mortality disparity between these cohorts. Significantly more CDI patients died compared to controls and these patients were excluded from their respective follow-up analyses (e.g., patients who died within 1 month were excluded from aging-related condition analyses at 1 month). These data suggest that if patients are fit enough to survive the CDI encounter in the short-term, they are not likely to develop other chronic conditions in the long-term compared to matched controls.

Analyses of the female subgroup showed lower rates of aging-related conditions compared to males. In short, women have lower rates of cardiovascular disease than men, though this varies based on the specific type of cardiovascular disease. A number of factors can impact this difference, including women taking more initiative with their general health and seeking preventive care (overall CVD), but taking longer to receive medical care for some events compared to men (e.g., acute coronary syndrome) as well as sex differences in the pharmacokinetics of cardiac drugs therapies (oral bioavailability, clearance, body fat distribution, plasma protein binding, and metabolism).[76] Likewise, there are sex differences seen in cancer susceptibility, which is one of the most consistent

findings in epidemiological studies of cancer to date.[77] The lifetime probability for developing cancer (including sex-specific cancers such as prostate and breast) is approximately 44.85% for males and 38.08% for females, despite males having a shorter life expectancy, with the same analysis showing that cancer mortality rates were also higher in males (223.0 vs. 153.2; ratio=1.46).[77] Considering these data, it is not surprising that after matching on aging-related conditions and analyzing females as a subgroup, rates were higher in males.

Additionally, sex differences are well documented in neuropsychiatric and neurodegenerative disorders, as females have lower rates of some neurological conditions (e.g., Parkinson's disease, 1:3.5 and amyotrophic lateral sclerosis, 1:1.6) but not others (e.g., Alzheimer's 3:1, and multiple sclerosis, 2-3:1), which are attributed in large part to direct and indirect immunomodulatory actions of many sex steroid hormones.[78] The rates of lower neurodegenerative disorders in this study is not surprising, despite the 3:1 ratio of Alzheimer's in females compared to males.

FRAILTY-ASSOCIATED CONDITIONS OUTCOMES

Frailty and its associated conditions were also investigated as secondary outcomes of this study. Rates of frailty-associated conditions were numerically higher in the CDI cohort for all follow-up periods but was only statistically significant at 1-year follow up. This is not surprising as CDI and control patients were matched on the VA frailty index at baseline and patients with certain pre-existing frailty conditions were excluded at

baseline. Frailty is considered a chronic condition that may take several months to years to develop after a medical event.[79] Similar to the aging condition analyses, we excluded patients who died at each follow-up period; thus, it is plausible that less frail patients ultimately survived resulting in diminished effect sizes for comparisons between the CDI and control groups over the follow-up periods.

As previously mentioned, most prior studies have evaluated short-term CDI outcomes, with few studies evaluating long-term outcomes. This creates a limitation on studying the effects of CDI on frailty and frailty-associated conditions over time. Frailty-associated conditions are commonly described in the CDI literature due to the acute nature of many of the symptoms and their sequelae which mimic frailty-associated conditions. For example, fluid and electrolyte imbalances are often seen quickly due to severe infectious diarrhea in a *C. difficile* positive patient resulting in dehydration. Therefore, correction of fluid and electrolyte imbalances are a common part of CDI management,[80] as well as monitoring weight loss while receiving care. Additionally, CDI patients often experience loss of appetite, nausea/vomiting, and abdominal bloating/tenderness following a CDI episode, particularly with repeat episodes; thus, poor nutrition may result in weight and muscle loss. A combination of these symptoms is what increases the risk of more severe frailty-associated diagnoses, such as coagulopathy, which was statistically significant at 1-year follow up ($p<0.0001$). This may also explain why the primary drivers of the differences in frailty between groups in this study were involuntary weight loss and anemia.

Considering the severity differences seen in community-onset CDI compared to hospital-onset CDI, it is not surprising that our CO-CDI only cohort experienced lower frailty rates. Mild or moderate infections that can be treated without hospitalization, or advanced treatments such as surgery, are associated with better health outcomes overall and therefore have better expected recovery.[81] Though hypervirulent strains (e.g., ribotype 027 or NAP1/B1/027) tend to cause more severe disease, we are unable to conclude the potential of these strains to cause increased risk of aging-related or frailty-associated condition development post-CDI due to lack of strain data in this study and the lack of research regarding long-term microbiota implications between strains.

Correlation analyses were performed to assess the potential relationship over time between the number of CDI episodes and VA frailty index. This was assessed at both the 12-month follow-up and 10-year follow-up for appropriate patients (i.e., only those with 10 years of data were included in the 10-year correlation). Number of CDI episodes was positively and significantly correlated with VA frailty index at 12 months ($p<0.0001$) and 10-years ($p<0.0001$), though there was little variability in both analyses in which VA FI could be attributed directly to number of CDI episodes. Furthermore, there was a positive association between the number of CDI episodes and the development of any frailty associated condition at 1-year ($p<0.0001$) and 10 years ($p<0.0001$). This "dose-response" relationship strengthens our hypothesis that CDI is associated with the development of frailty conditions by demonstrating that the more CDI episodes a patient has, the higher their risk for frailty.

Frailty and decreased functional status have been previously reported as independent predictors of CDI,[82] but also as predictors of recurrence within one year, morbidity, and mortality.[83-85] Considering the impact that CDI has on the host's frailty-associated variables as previously discussed, it is important to consider how frailty post-CDI will make the host vulnerable to multimorbidity, including an increased frailty index, and therefore, mortality. Using modified frailty indices, frailty has shown to be a predictor of mortality in those who developed more serious outcomes, such as colectomy.[85] In summary, frailty can continue to affect CDI patients, even after recovery, as shown by their increased risk of recurrent infection. Frailty and its associated conditions should be identified and followed in at-risk patients, even after recovery from infection.

STUDY STRENGTHS

There are several strengths of our study design. First, combined CDI patients and controls produced a sample size of 112,806 patients, which allowed for powerful statistical comparisons between groups. The VHA is the largest integrated healthcare system in the U.S., which gave us full medical record access for all outpatient and inpatient VHA encounters for each patient over the study period, as long as the patient remained active in the VHA system. In addition, this study utilized a combination of ICD-9-CM/ICD-10-CM codes, positive stool tests for CDI, and documentation of CDI therapy to improve accuracy of CDI classification and minimize misclassification bias.

Prior studies have shown that there is good correlation between *C. difficile* toxin assay results and ICD-9-CM codes (the sensitivity and specificity of ICD-9-CM codes are estimated to be 71 to 78% and >99%, respectively in comparison to microbiologic data),[48-50] further reducing the risk of misclassification bias. Finally, the retrospective cohort design provided us with the ability to study aging- and frailty-related outcomes simultaneously as opposed to focusing on a single study outcome over a longer period of time than would be possible with a prospective design.

LIMITATIONS

As this is a retrospective study, there are inherent limitations. The data may be subject to misclassification bias, as mentioned previously, and confounding due to the use of administrative coding from electronic health records for data collection. Specifically, ICD-9-CM and ICD-10 codes were used during the respective study years in which they were integrated into the VHA; however, changes in coding for diagnoses over time might result in the potential for misclassification of some diagnoses. We attempted to minimize these limitations with the use of robust methods to confirm CDI classification, as mentioned in the strengths section, as well as control for confounding using propensity score-matched cohorts. The use of the veteran-only data provided us with predominantly elderly and male patients. The findings may therefore not be generalizable to non-VHA care settings; however, a large sample size of elderly patients will hold some generalizability to the average CDI patient population. In addition, the large sample size allowed us to conduct subgroup analyses on underrepresented groups (e.g., females),

though some subgroup analyses were underpowered for bivariable and multivariable analyses. It is possible that veterans sought care outside of the VHA system and certain outpatient or inpatient visits will be missed. Next, in the study time period, few VHA facilities were reporting *C. difficile* strain type (e.g., ribotype 027); thus, we were unable to evaluate the impact of specific *C. difficile* strains and health outcomes. Despite this, we were able to capture other CDI characteristics (community- vs. hospital-onset and severity), strengthening the potential association between CDI characteristics and aging- and frailty-related outcomes. Next, it may be difficult to infer a causal relationship between CDI and health outcomes, particularly those that develop later in the follow-up period (e.g., 10 years) because many other factors could have occurred during follow-up to predispose the patient to the outcome. As a result, we carefully considered the rate of outcomes over the course of 10 years, as well as controlled for new comorbidities and other important factors in our propensity score matched cohorts at each follow-up period. Finally, although the size and scope of our cohort is a major strength, the sample size could result in over-powered statistical comparisons, whereby even small differences between groups (i.e., small effect size) result in statistically significant differences between groups. To address this, we included a team of clinician-scientists who were able to provide expert opinions on the clinical significance of associations identified.

CONCLUSIONS & FUTURE DIRECTIONS

Despite advances in infection prevention and antimicrobial stewardship, CDI continues to threaten public health, including that of U.S. veterans. In this large-scale

retrospective study, we found that CDI was an independent predictor of mortality in the short- and long-term; this association was significant and believed to be at least partially responsible for the lack of significant associations between CDI and aging-related and frailty-associated outcomes. Despite numerically higher rates, CDI was not a statistically significant predictor of aging-related conditions; however, CDI was associated with frailty at 12 months and there was an association between number of CDI episodes and frailty index at 12 months and 10 years.

Future directions of this research field should include two study paths: 1) prospectively measuring gut microbiome composition and recovery post-CDI while assessing the development of aging-related and frailty-associated outcomes to have stronger evidence of biological plausibility in regard to CDI increasing the risk of development of these conditions, and 2) evaluating interventions that can help mitigate mortality and the development of chronic conditions post-CDI.

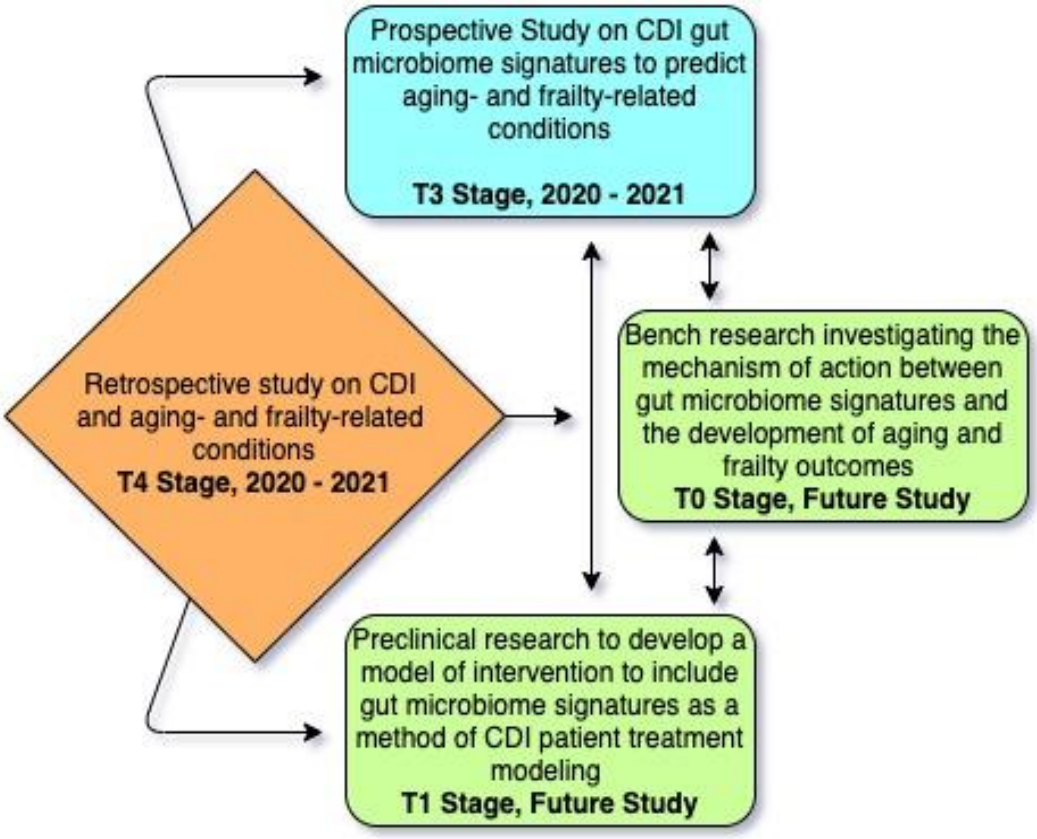
Overall, CDI prevention, effective treatment therapies, and recurrence avoidance should become and remain national level priorities in the Veterans Health Care System. With a high number of multimorbid patients, the VHA would benefit from preventing and adequately treating CDI as soon as possible, especially in high-risk patients. Additionally, the VHA should remain vigilant to current epidemic trends in CDI, as well as embrace new therapies as identified by continuously updated SHEA/IDSA *C. difficile* guidelines, including the use of fecal microbiota transplant in appropriate patient populations.

Chapter 7: Relevance to Translational Science

This research fulfilled the public health realm of the translational science spectrum, or the T4 phase as described in the accompanying figure below. In this stage of translational science research, we specifically pursued health outcomes research at the population level to determine the effects of CDI on aging and frailty development with the goal of generating new prevention, diagnosis, and treatment efforts. We intend to further pursue research at the T3 stage, which will include using the findings of this study to justify a prospective human study involving more in-depth gut microbiome research (clinical implementation, or T3 stage study), helping to guide basic scientists to determine more exact mechanisms of action regarding both CDI and the overall gut microbiome impact on healthy aging, jumpstarting research at the basic science and preclinical sciences research level (T0 and T1 stages).

While translational science is often explained as a linear process, working only in the direction of bench-to-bedside, this study importantly showed that clinical observations at the patient management level can be critical in identifying new areas of research with regard to the gut microbiome's complicated relationship with host disease, and ultimately, host aging processes. The results of this study will help build the foundation for new gut microbiome and aging research theories.

Figure 7.1. Translational science approach of the current study, and its anticipated impact on future research



Appendices

Appendix 1. ICD-9-CM and ICD-10-CM codes for comorbidities

Comorbidity	ICD-9-CM Code(s)	ICD-10-CM Code(s)
Myocardial infarction	410.x, 412.x	I21.x, I22.x, I25.2
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4 - 425.9, 428.x	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5 - I42.9, I43.x, I50.x, P29.0
Peripheral vascular disease	093.0, 437.3, 440.x, 441.x, 443.1 - 443.9, 447.1, 557.1, 557.9, V43.4	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5 - I42.9, I43.x, I50.x, P29.0
Cerebrovascular disease	362.34, 430.x - 438.x	G45.x, G46.x, H34.0, I60.x - I69.x
Dementia	290.x, 294.1, 331.2	F00.x - F03.x, F05.1, G30.x, G31.1
Chronic pulmonary disease	416.8, 416.9, 490.x - 505.x, 506.4, 508.1, 508.8	I27.8, I27.9, J40.x - J47.x, J60.x - J67.x, J68.4, J70.1, J70.3
Rheumatic disease	446.5, 710.0 - 710.4, 714.0 - 714.2, 714.8, 725.x	M05.x, M06.x, M31.5, M32.x - M34.x, M35.1, M35.3, M36.0
Peptic ulcer disease	531.x - 534.x	K25.x - K28.x
Mild liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570.x, 571.x, 573.3, 573.4, 573.8, 573.9, V42.7	B18.x, K70.0 - K70.3, K70.9, K71.3 - K71.5, K71.7, K73.x, K74.x, K76.0, K76.2 - K76.4, K76.8, K76.9, Z94.4
Diabetes without chronic complications	250.0 - 250.3, 250.8, 250.9	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9
Diabetes with chronic complications	250.4 - 250.7	E10.2 - E10.5, E10.7, E11.2 - E11.5, E11.7, E12.2 - E12.5, E12.7, E13.2 - E13.5, E13.7, E14.2 - E14.5, E14.7
Hemiplegia or paraplegia	334.1, 342.x, 343.x, 344.0 - 344.6, 344.9	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0 - G83.4, G83.9
Renal disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0 - 583.7, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x	I12.0, I13.1, N03.2 - N03.7, N05.2 - N05.7, N18.x, N19.x, N25.0, Z49.0 - Z49.2, Z94.0, Z99.2

Malignancy	140.x - 172.x, 174.x - 195.8, 200.x - 208.x, 238.6	C00.x - C26.x, C30.x - C34.x, C37.x - C41.x, C43.x, C45.x - C58.x, C60.x - C76.x, C81.x - C85.x, C88.x, C90.x - C97.x
Moderate or severe liver disease	456.0 - 456.2, 572.2- 572.8	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
Metastatic solid tumor	196.x - 199.x	C77.x - C80.x
AIDS/HIV	042.x - 044.x	B20.x - B22.x, B24.x
Hypertension	401-405	I10.x, I11.x, I12.x, I13.x, I15.x
Dyslipidemia	272	E78.0-E78.5
Obesity	278	E66.0x, E66.1, E66.2, E66.8, E66.9
GERD	530.11, 530.81	K21.0, K21.9
Transplant	V42, E878.0	Z94.xx
Inflammatory bowel disease	555.0-2, 555.9, 556.0-9	K50.XX, K51.XX, K52.3
Irritable bowel syndrome	564.1	K58.9
Schizophrenia	295.x, 293.81	F06.2, F20.x, F21
Depression	300.4, 301.1, 309.0 - 309.1, 311, 298.0	F31.4, F43.21, F32.9, F32.3 - F33.3
Bipolar disorder	296.0 - 296.6	F30.x, F31.x
Anxiety disorder	300.0, 300.2, 300.4, 309.2, 313.0	F06.4, F40.x, F41.x, F93.0 - F93.2
Post-traumatic stress disorder	309.81	F43.10, F43.12
Alcohol abuse	291.x, 303, 305	F10
Bacteremia	790.7	R78.81
Pneumonia	480.0-483.99, 485–487	J11.xx, J12.xx, J13.x-J16.x, J18.x
Skin infection	680-686	L01-05.XX, L08.XX, K12.2
Endocarditis	421.0, 421.1, 421.9, 424.9	I33.0X, I38, I39
Urinary tract infection	590-599	N10, N11.X, N30.XX, N39.0
Device-related infection	996.31, 996.62, 996.64, 999.31	T82.6, T82.7, T83.51, T83.6, T84.50, T84.60, T84.7, T85.71, T85.79
Acute respiratory infection	460-466	J00, J01.XX, J02-6.X, J20.X, J21.X
Intra-abdominal infections	562.00, 562.10, 562.11, 562.01, 562.13, 562.03, 542, 540-543, 540, 541, 567, 540.9	K35.XX, K36, K37, K57.XX, K65.X, K67, K68.1X
Shock	639.5, 785.52, 785.59	R57.0, R57.1, R57.8, R57.9, R65.21
Sepsis	020.2, 038.0-038.9, 995.91, 995.92	R65.2X, A41.X

Perforated intestine	569.83	K63.1
Ileus	560.1	K56.0, K56.4, K56.6X, K56.7
Megacolon	558.2, 564.7	K52.1, K59.31, K59.30
Acute renal failure	584, 586	N17.X

Appendix 2. CDI Retrospective Study Data Dictionary

Variable	Definition	Data Type/Menu
DEMOGRAPHICS		
Age	Date of first CDI encounter minus the date of birth (in years)	Continuous
Sex	Most common report of sex over the study period	Dichotomous (M,F)
Race	Most common report of race over the study period	Categorical (W,B,O)
Hispanic ethnicity	Most common report of Hispanic ethnicity over the study period	Dichotomous (1,0)
VHA priority group	Identified during first CDI encounter	Categorical (1-8)
VISN	Veterans Integrated Service Network during first encounter	Categorical
Prior hospitalization	Hospitalization within the 90-day period prior to encounter	Dichotomous (1,0)
EXPOSURES IN PAST YEAR		
Inpatient visits	Total # of inpatient stays in last year	Continuous
Outpatient visits	Total # of outpatient visits in last year	Continuous
Chronic dialysis	ICD-10 codes Z99.2 or N18.6 in last year	Dichotomous (1,0)
Long-term care residence	Residence in a long-term care facility (nursing home, skilled nursing facility, domiciliary) in the past year	Dichotomous (1,0)
MEDICATIONS IN PAST 90 DAYS		
Antibiotics	Any antibiotic prescribed 2+ days in 90 days preceding encounter (Table 1)	Dichotomous (1,0)
Gastric acid suppressants	Any GAS prescribed 2+ days in 90 days preceding encounter (Table 2)	Dichotomous (1,0)
Laxatives	Any laxative prescribed 2+ days in 90 days preceding encounter (Table 3)	Dichotomous (1,0)
Antidiarrheals	Any antidiarrheal prescribed 2+ days in 90 days preceding encounter (Table 4)	Dichotomous (1,0)
Opioid analgesics	Any opioid prescribed 2+ days in the 90 days preceding encounter (Table 5)	Dichotomous (1,0)
Cancer chemotherapy	Any chemo prescribed 2+ days in the 90 days preceding encounter (Table 6)	Dichotomous (1,0)
COMORBIDITIES IN PAST YEAR		
CDI	ICD-9 (008.45) or ICD-10 (A04.X) in the year preceding CDI encounter	Dichotomous (1,0)
Charlson comorbidities	Comorbidity in the year preceding CDI encounter (Table 7)	Dichotomous (1,0)
Selim comorbidities	Comorbidity in the year preceding CDI encounter (Table 7)	Dichotomous (1,0)
Other comorbidities	Comorbidity in the year preceding CDI encounter (Table 7)	Dichotomous (1,0)
Aging-related conditions	Condition in the year preceding CDI encounter (Table 7)	Dichotomous (1,0)

Frailty-associated diagnoses	Diagnosis in the year preceding CDI encounter (Table 7)	Dichotomous (1,0)
ENCOUNTER CHARACTERISTICS		
Treatment setting	Setting where CDI therapy began (CDI) or encounter occurred (controls)	Dichotomous (In,Out)
Severity indicators	Any severity indicator during the encounter (Table 7)	Dichotomous (1,0)
ICU admission	ICU admission any time during hospitalization	Dichotomous (1,0)
ICU <48 hours	ICU admission within first 48 hours of hospitalization	Dichotomous (1,0)
ICU ≥48 hours	ICU admission after first 48 hours of hospitalization	Dichotomous (1,0)
WBC ≥15 x10^9 cells/μL	White blood cell count ≥15 anytime during encounter	Dichotomous (1,0)
CRP ≥160 mg/L	C-reactive protein ≥160 anytime during encounter	Dichotomous (1,0)
Albumin <2.5 g/dL	Albumin <2.5 anytime during encounter	Dichotomous (1,0)
SCr >1.5 mg/dL	Serum creatinine >1.5 anytime during encounter	Dichotomous (1,0)
CDI therapies	Each CDI therapy prescribed for 2+ days during encounter	Dichotomous (1,0)
Any CDI therapy	CDI therapy started anytime during encounter (Table 8)	Dichotomous (1,0)
CDI therapy ≤48 hours	CDI therapy started outpatient or on inpatient day 1 or 2 (Table 8)	Dichotomous (1,0)
CDI therapy >48 hours	CDI therapy started on or after day 3 of hospitalization (Table 8)	Dichotomous (1,0)
HCFO-CDI	CDI therapy started on or after day 3 of hospitalization (Table 8)	Dichotomous (1,0)
CA-CDI	CDI therapy started outpatient or on inpatient day 1 or 2 (Table 8)	Dichotomous (1,0)
CO-HCFA-CDI	CDI therapy started outpatient or on inpatient day 1 or 2 + prior hospitalization	Dichotomous (1,0)
Concomitant infection	Any infection documented during the encounter (Table 7)	Dichotomous (1,0)
OUTCOMES AT 30 DAYS FOLLOW-UP		
Mortality	Death within 30 days of CDI treatment/encounter end date	Dichotomous (1,0)
Recurrence	CDI ICD code within 30 days of CDI treatment end date + 3 day gap	Dichotomous (1,0)
Aging-related conditions	Any condition within 30 days of CDI treatment/encounter end date (Table 7)	Dichotomous (1,0)
Frailty-associated diagnoses	Any diagnosis within 30 days of CDI treatment/encounter end date (Table 7)	Dichotomous (1,0)
VA Frailty Index Score	Calculated as # of deficits divided by 31 (Table 8) within 30 days of CDI treatment/encounter end date	Continuous (0 - 1)
OUTCOMES AT 60 DAYS FOLLOW-UP		
Mortality	Death within 60 days of CDI treatment/encounter end date	Dichotomous (1,0)
Recurrence	CDI ICD code within 60 days of CDI treatment end date + 3 day gap	Dichotomous (1,0)
Aging-related conditions	Any condition within 60 days of CDI treatment/encounter end date (Table 7)	Dichotomous (1,0)
Frailty-associated diagnoses	Any diagnosis within 60 days of CDI treatment/encounter end date (Table 7)	Dichotomous (1,0)

VA Frailty Index Score	Calculated as # of deficits divided by 31 (Table 8) within 60 days of CDI treatment/encounter end date	Continuous (0 - 1)
OUTCOMES AT 90 DAYS FOLLOW-UP		
Mortality	Death within 90 days of CDI treatment/encounter end date	Dichotomous (1,0)
Recurrence	CDI ICD code within 90 days of CDI treatment end date + 3 day gap	Dichotomous (1,0)
Aging-related conditions	Any condition within 90 days of CDI treatment/encounter end date (Table 7)	Dichotomous (1,0)
Frailty-associated diagnoses	Any diagnosis within 90 days of CDI treatment/encounter end date (Table 7)	Dichotomous (1,0)
VA Frailty Index Score	Calculated as # of deficits divided by 31 (Table 8) within 90 days of CDI treatment/encounter end date	Continuous (0 - 1)
EXPOSURES AT 1 YEAR FOLLOW-UP		
Inpatient visits	Total # of inpatient stays within 1 year of encounter end date	Continuous
Outpatient visits	Total # of outpatient visits within 1 year of encounter end date	Continuous
Chronic dialysis	ICD-10 codes Z99.2 or N18.6 within 1 year of encounter end date	Dichotomous (1,0)
Long-term care residence	Residence in a long-term care facility (nursing home, skilled nursing facility, domiciliary) within 1 year of encounter end date	Dichotomous (1,0)
Number of CDI episodes	Total # of CDI encounters (ICD-9 008.45 or ICD-10 A04) within 1 year of first encounter end date	Continuous
COMORBIDITIES AT 1 YEAR FOLLOW-UP		
Charlson comorbidities	Comorbidity within 1 year of encounter end date (Table 7)	Dichotomous (1,0)
Selim comorbidities	Comorbidity within 1 year of encounter end date (Table 7)	Dichotomous (1,0)
Other comorbidities	Comorbidity within 1 year of encounter end date (Table 7)	Dichotomous (1,0)
MEDICATIONS AT 1 YEAR FOLLOW-UP		
Antibiotics	Any antibiotic within 1 year of CDI treatment/encounter end date (Table 1)	Dichotomous (1,0)
Gastric acid suppressants	Any GAS within 1 year of CDI treatment/encounter end date (Table 2)	Dichotomous (1,0)
Laxatives	Any laxative within 1 year of CDI treatment/encounter end date (Table 3)	Dichotomous (1,0)
Antidiarrheals	Any antidiarrheal within 1 year of CDI treatment/encounter end date (Table 4)	Dichotomous (1,0)
Opioid analgesics	Any opioid within 1 year of CDI treatment/encounter end date (Table 5)	Dichotomous (1,0)
Cancer chemotherapy	Any chemo within 1 year of CDI treatment/encounter end date (Table 6)	Dichotomous (1,0)
OUTCOMES AT 1 YEAR FOLLOW-UP		
Mortality	Death within 1 year of CDI treatment/encounter end date	Dichotomous (1,0)

Recurrence	CDI ICD code within 1 year of CDI treatment end date + 3 day gap	Dichotomous (1,0)
Aging-related conditions	Any condition within 1 year of CDI treatment/encounter end date (Table 7)	Dichotomous (1,0)
Frailty-associated diagnoses	Any diagnosis within 1 year of CDI treatment/encounter end date (Table 7)	Dichotomous (1,0)
VA Frailty Index Score	Calculated as # of deficits divided by 31 (Table 8) within 1 year of CDI treatment/encounter end date	Continuous (0 - 1)
EXPOSURES AT 10 YEAR FOLLOW-UP		
Inpatient visits	Total # of inpatient stays within 10 years of encounter end date	Continuous
Outpatient visits	Total # of outpatient visits within 10 years of encounter end date	Continuous
Chronic dialysis	ICD-10 codes Z99.2 or N18.6 within 10 years of encounter end date	Dichotomous (1,0)
Long-term care residence	Residence in a long-term care facility (nursing home, skilled nursing facility, domiciliary) within 10 years of encounter end date	Dichotomous (1,0)
Number of CDI episodes	Total # of CDI encounters (ICD-9 008.45 or ICD-10 A04) within 10 years of first encounter end date	Continuous
COMORBIDITIES AT 10 YEAR FOLLOW-UP		
Charlson comorbidities	Comorbidity within 10 years of encounter end date (Table 7)	Dichotomous (1,0)
Selim comorbidities	Comorbidity within 10 years of encounter end date (Table 7)	Dichotomous (1,0)
Other comorbidities	Comorbidity within 10 years of encounter end date (Table 7)	Dichotomous (1,0)
MEDICATIONS AT 10 YEAR FOLLOW-UP		
Antibiotics	Any antibiotic within 10 years of CDI treatment/encounter end date (Table 1)	Dichotomous (1,0)
Gastric acid suppressants	Any GAS within 10 years of CDI treatment/encounter end date (Table 2)	Dichotomous (1,0)
Laxatives	Any laxative within 10 years of CDI treatment/encounter end date (Table 3)	Dichotomous (1,0)
Antidiarrheals	Any antidiarrheal within 10 years of CDI treatment/encounter end date (Table 4)	Dichotomous (1,0)
Opioid analgesics	Any opioid within 10 years of CDI treatment/encounter end date (Table 5)	Dichotomous (1,0)
Cancer chemotherapy	Any chemo within 10 years of CDI treatment/encounter end date (Table 6)	Dichotomous (1,0)
OUTCOMES AT 10 YEAR FOLLOW-UP		
Mortality	Death within 10 years of CDI treatment/encounter end date	Dichotomous (1,0)
Recurrence	CDI ICD code within 10 years of CDI treatment end date + 3 day gap	Dichotomous (1,0)
Aging-related conditions	Any condition within 10 years of CDI treatment/encounter end date (Table 7)	Dichotomous (1,0)

Frailty-associated diagnoses	Any diagnosis within 10 years of CDI treatment/encounter end date (Table 7)	Dichotomous (1,0)
VA Frailty Index Score	Calculated as # of deficits divided by 31 (Table 8) within 10 years of CDI treatment/encounter end date	Continuous
Time to mortality	Date of death minus date of CDI treatment/encounter end date plus one (days)	Continuous

Appendix 3. Non-CDI antibiotics

Generic Name	**Brand Name(s)**
Penicillin G	Pfizerpen
Penicillin VK	Pen-vee K
Ampicillin	Principen
Amoxicillin	Amoxil
Cloxacillin	Cloxapen
Dicloxacillin	Dynapen
Nafcillin	Nallpen, Unipen
Oxacillin	Bactocill
Amoxicillin-clavulanate	Augmentin
Ticarcillin disodium-clavulanate	Timentin
Piperacillin-tazobactam	Zosyn
Piperacillin	Pipracil
Ampicillin-sulbactam	Unasyn
Cefadroxil	Duricef
Cephalexin	Keflex
Cefazolin	Ancef
Cefaclor	Ceclor, Raniclor
Cefprozil	Cefzil
Cefuroxime axetil	Zinacef, Ceftin
Cefoxitin	Mefoxin
Cefdinir	Omnicef
Cefixime	Suprax
Cefotaxime	Claforan
Cefpodoxime	Vantin
Ceftibuten	Cedax
Ceftizoxime	Cefizox
Ceftriaxone	Rocephin
Ceftazidime	Fortaz
Cefepime	Maxipime
Ceftaroline fosamil	Teflaro
Imipenem/cilastatin	Primaxin

Meropenem	Merrem
Ertapenem	Invanz
Doripenem	Doribax
Colistin	Coly-mycin
Polymyxin B	Aerosporin
Azithromycin	Zithromax
Clarithromycin	Biaxin
Erythromycin	Erythrocin
Telithromycin	Ketek
Moxifloxacin	Avelox
Ciprofloxacin	Cipro
Levofloxacin	Levaquin
Gatifloxacin	Zymaxid, Zymar
Trovafloxacin	Trovan
Gemifloxacin	Factive
Linezolid	Zyvox
Trimethoprim-sulfamethoxazole	Bactrim, Septra
Vancomycin (IV)	Vancocin
Metronidazole	Flagyl
Gentamicin	Garamycin
Tobramycin	Nebcin
Amikacin	Amikin
Aztreonam	Azactam
Nitrofurantoin	Macrobid, Macrodantin
Televancin	Vibativ
Clindamycin	Cleocin
Daptomycin	Cubicin
Doxycycline	Doryx, Vibramycin, Oracea
Minocycline	Minocin, Dynacin
Tetracycline	Sumycin
Fosfomycin	Monurol
Quinupristin/dalfopristin	Synercid
Tigecycline	Tigacyl

Appendix 4. Gastric acid suppressant medications

Generic name	Brand name(s)
Omeprazole	Prilosec, Zegerid
Lansoprazole	Prevacid
Dexlansoprazole	Kapidex, Dexilant
Esomeprazole	Nexium, Esotrex
Pantoprazole	Protonix
Rabeprazole	Aciphex
Ranitidine	Zantac
Nizatidine	Axid
Famotidine	Pepcid
Cimetidine	Tagamet
Calcium carbonate	Tums, Rolaids
Magnesium hydroxide	Rolaids, Milk of Magnesia
Magnesium oxide	Mag-Ox, MagGel, Uro-Mag, Mag-200
Bismuth subsalicylate	Pepto Bismol, Kaopectate

Appendix 5. Laxatives

Generic name	Brand name
Magnesium citrate	Phillips' Milk of Magnesia
Magnesium hydroxide	Phillips' Milk of Magnesia
Magnesium oxide	Prepopik
Magnesium sulfate	Suprep
Sodium phosphate	Fleet Enema
Senna	Senokot
Bisacodyl	Dulcolax
Castor oil	
Methylcellulose	Citrucel
Psyllium	Metamucil
Wheat dextrin	Benefiber
Mineral oil	
Docusate	Peri-Colace, Colace, Surfak
Glycerin	
Lactulose	
Polyethylene glycol 3350 (PEG)	GlycoLax, MiraLax
Sorbitol 70%	
Linaclotide	Linzess
Lubiprostone	Amitiza
Alvimopan	Entereg
Methylnaltrexone	Relistor
Naloxegol	Movantik

Appendix 6. Anti-diarrheals

Generic Name	Brand Name
Atropine and diphenoxylate	Lomotil
Bismuth subsalicylate	Bismatrol, Diotame, Geri-Pectate, Kao-Tin, Peptic Relief, Pepto-Bismol, Pink Bismuth, Stomach Relief
Loperamide	Anti-Diarrheal, Diamode, Immodium A-D, Loperamide A-D

Appendix 7. Opioid analgesics

Generic Name
Morphine
Hydromorphone
Codeine
Oxymorphone/oxycodone
Fentanyl/meperidine
Methadone
Buprenorphine
Pentazocine
Nalbuphine
Butorphanol
Dexocine
Naloxone/naltrexone
Hydrocodone

Appendix 8. Cancer chemotherapy

Class	Generic Name	Brand Name(s)
Alkylating agent	Cyclophosphamide	Cytoxan
	Ifosfamide	Ifex
	Temozolomide	Temodar
	Dacarbazine	DTIC
	Melphalan	Alkeran
	Busulfan	Myleran
	Lomustine	CeeNU
	Carmustine	BiCNU, Gliadel
	Procarbazine	Matulane
	Chlorambucil	Leukeran
	Mechlorethamine	Mustargen
	Streptozosin	Zanosar
	Altretamine	Hexalen
	Thiotepa	Thioplex
	Bendamustine	Treanda
	Estramustine	Emcyt

Anthracyclines	Doxorubicin	Adriamycin
	Doxorubicin liposomal	Doxil
	Epirubicin	Ellence
	Idarubicin	Idamycin
	Daunorubicin	Cerubidine
	Daunorubicin liposomal	DaunoXome
	Mitoxantrone	Novantrone
	Valrubicin	Valstar
Platinum analogs	Cisplatin	Platinol
	Carboplatin	Paraplatin-AQ
	Oxaliplatin	Eloxatin
Folate antimetabolites	Methotrexate	Trexall, Otrexup, Rasuvo, Rheumatrex
	Pemetrexed	Alimta
	Pralatrexate	Folotyn
	Ralitrexed	Tomudex
Pyrimidine analogs	Capecitabine	Xeloda
	Cytarabine	Ara-C, Cytosar
	Floxuridine	FUDR
	Fluorouracil, 5-FU	Adrucil
	Gemcitabine	Gemzar
Taxanes	Paclitaxel	Taxol
	Paclitaxel protein bound	Abraxane
	Docetaxel	Taxotere
	Cabazitaxel	Jevtana
Vinka alkaloids	Vincristine	Vincasar, Oncovin
	Vincristine liposomal	Marqibo
	Vinblastine	Velban
	Vindesine	.
	Vinorelbine	Navelbine
Topoisomerase I inhibitors	Irinotecan	Camptosar
	Irinotecan liposomal	Onivyde
	Topotecan	Hycamtin
Topoisomerase II inhibitors	Etoposide	VePesid
	Teniposide	Vumon
Epothilone	Ixabepilone	Ixempra
Miscellaneous agents	Tretinoin	All-trans retinoic acid, ATRA Vesanoid
	Arsenic trioxide	Trisenox

	L-Asparaginase	Elspar
	Asparaginase	Erwinaze
	Pegaspargase	Oncaspar
	Bleomycin	.
	Mitomycin	Mutamycin
Antiandrogen	Bicalutamide	Casodex
	Flutamide	Eulexin
	Nilutamide	Nilandron
	Degarelix	Firmagon
	Abiraterone acetate	Zytiga
	Enzalutamide	Xtandi
Antiandrogen-Antiestrogen	Goserelin	Zoladex
	Leuprolide	Lupron, Eligard, Viadur
	Histrelin	Vantas
	Triptorelin	Trelstar
Aromatase inhibitor	Anastrozole	Arimidex
	Letrozole	Femara
	Exemestane	Aromasin
Antiestrogens	Tamoxifen	Soltamox
	Fulvestrant	Faslodex
	Raloxifene	Evista
Tyrosine Kinase inhibitors	Lapatinib	Tykerb
	Alectinib	Alecensa
	Brigatinib	Alunbrig
	Sunitinib	Sutent
	Vandetanib	Caprelsa
	Cabozantinib	Cabometyx, Cometriq
	Pazopanib	Votrient
	Sorafenib	Nexavar
	Axitinib	Inlyta
	Imatinib	Gleevec
	Nilotinib	Tasigna
	Dasatinib	Sprycel
	Ponatinib	Iclusig
	Bosutinib	Bosulif
	Lenvatinib	Lenvima
	Midostaurin	Rydapt
	Osimertinib	Tagrisso
	Regorafenib	Stivarga
	Erlotinib	Tarceva
	Afatinib	Gilotrif
	Ceritinib	Zykadia

	Crizotinib	Xalkori
	Vemurafenib	Zelboraf
	Dabrafenib	Tafinlar
	Gefitinib	Iressa
	Ibrutinib	Imbruvica
mTOR inhibitors	Everolimus	Afinitor
	Temsirolimus	Torisel
MEK1 and MEK2 inhibitor	Trametinib	Mekinist
	Cobimetinib	Cotellic
Immunomodulators	Lenalidomide	Revlimid
	Pomalidomide	Pomalyst
	Thalidomide	Thalomid
	Interferon Alfa-2b	Intron A
	Peginterferon Alfa-2b	PegIntron
Proteasome inhibitors	Bortezomib	Velcade
	Carfilzomib	Kyprolis
	Ixazomib	Ninlaro

Appendix 9. Comorbidities/diagnosis

Comorbidity	**ICD-9-CM Code(s)**	**ICD-10-CM Code(s)**
CHARLSON COMORBIDITIES		
Myocardial infarction	410.x, 412.x	I21.x, I22.x, I25.2
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4 - 425.9, 428.x	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5 - I42.9, I43.x, I50.x, P29.0
Peripheral vascular disease	093.0, 437.3, 440.x, 441.x, 443.1 - 443.9, 447.1, 557.1, 557.9, V43.4	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5 - I42.9, I43.x, I50.x, P29.0
Cerebrovascular disease	362.34, 430.x - 438.x	G45.x, G46.x, H34.0, I60.x - I69.x
Dementia	290.x, 294.1, 331.2	F00.x - F03.x, F05.1, G30.x, G31.1
Chronic pulmonary disease	416.8, 416.9, 490.x - 505.x, 506.4, 508.1, 508.8	I27.8, I27.9, J40.x - J47.x, J60.x - J67.x, J68.4, J70.1, J70.3
Rheumatic disease	446.5, 710.0 - 710.4, 714.0 - 714.2, 714.8, 725.x	M05.x, M06.x, M31.5, M32.x - M34.x, M35.1, M35.3, M36.0
Peptic ulcer disease	531.x - 534.x	K25.x - K28.x
Mild liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570.x, 571.x, 573.3, 573.4, 573.8, 573.9, V42.7	B18.x, K70.0 - K70.3, K70.9, K71.3 - K71.5, K71.7, K73.x, K74.x, K76.0, K76.2 - K76.4, K76.8, K76.9, Z94.4
Diabetes without complications	250.0 - 250.3, 250.8, 250.9	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9,

		E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9
Diabetes with complications	250.4 - 250.7	E10.2 - E10.5, E10.7, E11.2 - E11.5, E11.7, E12.2 - E12.5, E12.7, E13.2 - E13.5, E13.7, E14.2 - E14.5, E14.7
Hemiplegia or paraplegia	334.1, 342.x, 343.x, 344.0 - 344.6, 344.9	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0 - G83.4, G83.9
Renal disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0 - 583.7, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x	I12.0, I13.1, N03.2 - N03.7, N05.2 - N05.7, N18.x, N19.x, N25.0, Z49.0 - Z49.2, Z94.0, Z99.2
Malignancy	140.x - 172.x, 174.x - 195.8, 200.x - 208.x, 238.6	C00.x - C26.x, C30.x - C34.x, C37.x - C41.x, C43.x, C45.x - C58.x, C60.x - C76.x, C81.x - C85.x, C88.x, C90.x - C97.x
Moderate/severe liver disease	456.0 - 456.2, 572.2- 572.8	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
Metastatic solid tumor	196.x - 199.x	C77.x - C80.x
AIDS/HIV	042.x - 044.x	B20.x - B22.x, B24.x
OTHER COMORBIDITIES		
Hypertension	401-405	I10.x, I11.x, I12.x, I13.x, I15.x
Dyslipidemia	272	E78.0-E78.5
Obesity	278	E66.0x, E66.1, E66.2, E66.8, E66.9
GERD	530.11, 530.81	K21.0, K21.9
Transplant	V42, E878.0	Z94.xx
Inflammatory bowel disease	555.0-2, 555.9, 556.0-9	K50.XX, K51.XX, K52.3
Irritable bowel syndrome	564.1	K58.9
SELIM COMORBIDITIES		
Schizophrenia	295.x, 293.81	F06.2, F20.x, F21
Depression	300.4, 301.1, 309.0 - 309.1, 311, 298.0	F31.4, F43.21, F32.9, F32.3 - F33.3
Bipolar disorder	296.0 - 296.6	F30.x, F31.x
Anxiety disorder	300.0, 300.2, 300.4, 309.2, 313.0	F06.4, F40.x, F41.x, F93.0 - F93.2
Post-traumatic stress disorder	309.81	F43.10, F43.12
Alcohol abuse	291.x, 303, 305	F10
CONCOMITANT INFECTIONS		
Bacteremia	790.7	R78.81
Pneumonia	480.0-483.99, 485–487	J11.xx, J12.xx, J13.x-J16.x, J18.x
Skin infection	680-686	L01-05.XX, L08.XX, K12.2
Endocarditis	421.0, 421.1, 421.9, 424.9	I33.0X, I38, I39
Urinary tract infection	590-599	N10, N11.X, N30.XX, N39.0

Device-related infection	996.31, 996.62, 996.64, 999.31	T82.6, T82.7, T83.51, T83.6, T84.50, T84.60, T84.7, T85.71, T85.79
Acute respiratory infection	460-466	J00, J01.XX, J02-6.X, J20.X, J21.X
Intra-abdominal infections	562.00, 562.10, 562.11, 562.01, 562.13, 562.03, 542, 540-543, 540, 541, 567, 540.9	K35.XX, K36, K37, K57.XX, K65.X, K67, K68.1X
SEVERITY INDICATORS		
Shock	639.5, 785.52, 785.59	R57.0, R57.1, R57.8, R57.9, R65.21
Sepsis	020.2, 038.0-038.9, 995.91, 995.92	R65.2X, A41.X
Perforated intestine	569.83	K63.1
Ileus	560.1	K56.0, K56.4, K56.6X, K56.7
Megacolon	558.2, 564.7	K52.1, K59.31, K59.30
Acute renal failure	584, 586	N17.X
AGING-RELATED CONDITIONS		
Neurodegenerative diseases	290, 294, 331-2	G20, G30-1, F01-3
Cardiovascular diseases	410, 412, 430-438	I21, I63.0-I63.9
FRAILTY-ASSOCIATED DIAGNOSES		
Coagulopathy	286.0-286.9	D65-D69
Involuntary weight loss	783.21	R63.4
Fluid & electrolyte imbalance	276.9	E87
Anemia	280.0-285.9	D60-D64
Falls	V15.88	Z91.81
Fracture	800.0-829.9	S02, S22, S32, M48

Appendix 10. CDI therapies

Generic Name	**Brand Name(s)**
Metronidazole (oral or IV)	Flagyl
Vancomycin (oral)	Vancocin
Fidaxomicin	Dificid
Rifaximin	Xifaxan
Nitazoxanide	Alinia
Saccharomyces boulardii	Florastor
Lactobacillus	Acidophilus
Bifidobacterium	Align
Intravenous immune globulin	Flebogamma, Carimune, Gammagard, Gamunex, Iveegam, Octagam, Polygam
Fecal transplantation	44705 (CPT)

Appendix 11. VA Frailty Index Score (VA-FI) variable list and assigned patient values.

A value of 1 is assigned if the variable is present in the patient's chart at the point of preview. A value of 0 is assigned if the variable is not present. (Unless otherwise stated). The final coding equation will include the number of variables present divided by the total number of variables in the index, for example:

If a patient has 10 of the 31 variables (deficits) present, they would be coded as: 10/31 = 0.33, qualifying them as moderately frail based on the validated groups we will be using (Table 10 below). In analyses comparing frail vs. non-frail, frailty should be considered any score of 0.21 or greater.

VA Frailty Index Variable	**ICD-9-CM Code(s)**	**ICD-10-CM Code(s)**
Anemia	280.0-285.9	D50-D64.9
Atrial Fibrillation	427.3, 427.31	I48.x
Cancer (any except basal cell skin cancer)	140 - 200 EXCLUDING: 173.01, 173.11, 173.21, 173.31, 173,41, 173.51, 173.61, 173.71, 173,81, 173.91	ALL C00 - C96 EXCLUDING: C44.01, C44.111, C44.211, C44.310, C44.311, C44.319, C44.41, C44.510, C44.511, C44.519, C44.611, C44.711, C44.81, C44.91
Cerebrovascular disease: Stroke or TIA	362.34 434.x 435.9	H34.00 I67.84 G45.9
Coronary Artery Disease: MI, CABG, or PCI	410.x, 412.x, 414.04, 429.2, 429.5 429.7, V45.82	I21.x, I22.x, I25.10, I25.2, I51.1, I25.709, I25.810, Z98.61
Diabetes	250.00, 250.02, 250.10, 250.12, 250.20, 250.22 250.30, 250.32, 250.40, 250.42, 250.50, 250.52 250.60, 250.62, 250.70, 250.72, 250.80, 250.82 250.90, 250.92	E11.9, E11.65, E11.69, E13.10, E11.00, E11.01, E11.641, E11.29, E11.21, E11.311, E11.319, E11.36, E11.39, E11.40, E11.51, E11.51, E11.618, E11.620, E11.621, E11.622, E11.628, E11.630, E11.638, E11.649, E11.8
Heart Failure (diastolic or systolic)	428.x, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93	I50.x, I11.0, I13.0, I13.2
Hypertension	401 - 405	I10.x, I11.x, I12.x, I13.x, I15.x
Kidney Disease (Chronic Kidney Disease code = 0.5,	Chronic Kidney Disease (receives value of 0.5): 250.4,	Chronic Kidney Disease (receives value of 0.5): I12.0, I12.9, I13.0, I13.1,

Dialysis code =1)	403.00, 403.10, 403.90, 404.00, 404.01 404.10 - 404.11, 404.90, 404.91, 585 - 588, 582.x Dialysis: 403.01, 403.11, 403.91, 404.02 - 404.03, 404.12 - 404.13, 404.92 - 404.93, V42, V56, V45.1, E879.1	N03.2 - N03.7, N05.2 - N05.7, N18.x, N19.x, N25.x, Z94.0, Dialysis: I13.11, I13.2, Z99.2, Z49.0 - Z49.2
Liver Disease or Cirrhosis	570 - 571, 572.2, 572.3, 572.8, 573 006.3, 070.x, V42.7	B18.x, K70.x - K77.x, Z94.4 A06.4, B18 - B19, Z94.4
Lung disease: COPD or Asthma	490 - 496, 510	J41.x, J44.x, J45.x
Thyroid Disease	240, 241, 242, 244 - 245, 246.0, 246.3 - 246.9	E00 - E07
Osteoporosis or osteoporosis related fracture (vertebral fractures)	733.0, 733.13	M80, M81, M82, M84
Incontinence	625.6, 787.6, 788.3, 788.91	N39.3, N39.4, R39.8
Arthritis (rheumatoid arthritis or osteoarthritis)	274, 446.5, 710.9, 714.0 - 714.2, 714.4, 714.89, 714.9, 715, 716.1 - 716.3, 716.5 - 716.6, 716.8 - 716.9, 725	M05 - M09, M10.x, M12, M13, M31.6, M35.3, M35.9
Use of Durable Medical Equipment (CPT/HCPCS CODES)	E0000, E0100, E0105, E0130, E0135, E014X, E0153-E0159, E016X, E0170-E0171, E0240, E0245, E0247-E0248, E0291, E0293, E0295, E0297, E0303-E0304, E0621, E0625, E0630, E0637-E0638, E0641-E0642, E095X, E0961, E0966-E0967, E0790, E0972-E0979, E0981-E0986, E0988, E0990-E0993, E0995, E1002- E1012, E1014-E1018, E1028-E1031, E1035-E1036, E1038-E1039, E1065-E1066, E1069, E1160-E1161, E1220-E1228, E1230-E1238, E1296-E1298, E220X, E2210-E2215, E2218- E2222, E2224-E2228, E2231, E2291, E2293-E2294, E2300-E2301, E2310-E2311, E232X, E2330-E2331, E2340-E2343, E2350-E2351, E2358-E2359, E236X, E2370-E2378, E238X, E2390-E2397, E260X, E261X, E262X, E2630-E2633, K000X, K002X, K003X, K004X, K008X, K0050- K0058, K0062-K0063, K0069-K0073, K0077, K0079, K008X, K0098, K0103, K0105, K0107-K0108, K0195, K0460-K0461, K065X, K066X, K0800-K0802, K0806-K0808, K0812-K0816, K082X, K0830-K0831, K0835-K0843, K0848-K0849, K085X, K0860-K0864, K0868-K0871, K0877-K0880, K0884-K0886, K0898-K0900, T1000-T1005, T1019-T1022, T1030-T1031	

Fall or Fall related diagnoses: Hip fractures Or subdural hematoma Or subarachnoid hematoma	430, 733.14, 733.96, 800 - 801, 803, 835, 852, E880, E884.2 - E884.9, E885.9, E887, E888, V15.88,432.1	Z91.81, I60.9, I62.00, M84.459A, M84.359A, W19.XXXA, Z98.1, S06.6, S06.7
Fatigue	780.71, 780.79	R53.x, G93.3
Gait Abnormality or difficulty walking	781.2 - 781.4, 719.7	R26.x, R27.0, R27.8, R27.9, R29.5
Parkinson's Disease and Tremors	332.x, 333.1	G20.x, R25.1, G25.0 - G25.2
Peripheral vascular disease or Intermittent claudication	440 - 444, 447, 451 - 453, 557	170.x - I74.x, I77.x, I80.x - I82.x, I73.9, K55.0
Muscular wasting and disuse atrophy, cachexia, or debility	307.1, 728.2, 728.87, 783, 799.3 - 799.4	F50.00, M62.5, M62.81, R63.0, R64, R54, R53.81
Hearing Impairment/Hearing Aid	388.0 - 388.2, 389.9 , V53.2	H91.90, H91.23, Z46.1, Z97.4
Peripheral Neuropathy	250.7, 337.00, 337.09, 337.1, 356.4, 356.8, 357.1 - 357.7, 356.9	E11.51, H47.10, G90.09, G99.0, G60.3, G60.8, G63, E08.42, E09.42, E10.42, E11.42, E13.42, G62.0 - G62.2, G60.9
Vision Comorbidity (macular degeneration, glaucoma, blindness)	362.50-362.53,365.05-365.13, 365.2 - 365.7, 365.81-365.82, 365.89, 365.9, 368.30-368.31, 368.4, 368.60, 368.62-368.69, 368.7 - 368.9, 377.75, 369.x	H35.3x, H40, H53.60 - H53.69, H53.8 - H53.9, H47.619, H42, H54
Dementias (Alzheimer's, Vascular, Lewy Body, Pick's disease, Mild Cognitive Impairment, etc.)	290.0 - 290.4, 291.1 - 291.2, 293.0 - 293.1, 294.8 - 294.9, 331.0, 331.10 - 331.11, 331.82 - 331.83, 331.92, 333.4, 438.0, 780.09, 780.93, 799.5	F00 - F09, F10.96, F10.27, G30.9, G31.01, G31.83 - G31.84, G10, I69.91, R40.0, R40.1, R41.2 - R41.3
Anxiety	293.84, 300.0 - 300.1, 309.21, 309.24, 309.28	F06.4, F40.x, F41.x, F93.0 - F93.2, F43.22 - F43.23
Depression or Bipolar	296, 298.0, 309.0 - 309.1, 311	F31.4, F43.21, F32.9, F32.3, F33.3 F30.x, F31.x
Chronic Pain	338.29, 724.5, 338.4	G89.2x, M54.89, M54.9, G89.4
Failure to thrive	783.7	R62.7
Weight loss in the past year	783.2	R63.4

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